

The New England Journal of Medicine

Formerly the Boston Medical and Surgical Journal

Established 1823

Published by the Massachusetts Medical Society under the Jurisdiction of
The Committee on Publications

VOLUME 236

JANUARY-JUNE, 1947

8 Fenway, Boston 15

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KEY TO ABBREVIATIONS

c — correspondence
cr — case record
e — editorial
ma — medicolegal abstract

mdph — Massachusetts Department of Public Health
mms — Massachusetts Medical Society
mp — medical progress
misc — miscellany

mr — meeting report
n — notice
o — obituary
* — original article

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 HILL, W R 645 - c
 HIRSH, H L 314*
 HOAGLAND, C L 891*
 HOEPRICH, P D 43 - c
 HOFFMANN, R 933*
 HOLDEN, E M 796*
 HOMANS, J 196 - mms
 HOPKINS, F S 530*
 HOWE, C 741*
 HUEBNER, R J 552 - c
 HUGGINS, C 885*
 HURWITT, E S 20*

I

INGALLS, T H 437*
 INGRAHAM, F D 362, 402 - mp

J

JACOBSON, B 371, 760 - cr
 JONES, C M 255, 955 - cr
 JONES, S H 729*
 JOSLIN, E P 474 - mp

K

KAUFMAN, S B 783*
 KELLY, E H 741*
 KILHAM, L 969*
 KILROY, E A 64*
 KING, D S 407 - cr
 KOPROWSKI, H 647*
 KRUGER, S 63*
 KUBIK, C S 36, 109, 112 - cr
 KUNKEL, H G 891*

L

LAFORET, E G 534*
 LAHEY, F H 46*, 551 - c
 LAMPHIER, T A 166, 318*
 LEECH, C B 327 - cr
 LENZNER, A R. 500*
 LEWIS, J H 351*
 LINDEMANN, E 783*
 LINGLEY, J R 112 - cr
 LLOYD, C W 737*
 LOCKE, A W 768 - c
 LOCKIE, L M 500*
 LOMAN, J 100*
 LORENZEN, F J 933*
 LOWE, C U 658*
 LYNCH, C L, JR 534

M

MACAUSLAND, W R 97*
 MAIRE, E D 1*
 MALLORY, T B 438 - mp
 MANNING, M J 337 - c
 MARSHALL, S F 95*
 MATSON, D D 362, 402 - mp
 MCGINN, S 806 - cr
 MCKITTRICK, J B 412, 716 - cr
 MCKITTRICK, L S 545 - cr, 921 - mms
 MEADS, M 862*
 MELKON, E A 940*
 METCOFF, J 26, 68 - mp
 MICHELSEN, J 289, 989 - cr
 MILLER, C B 542 - cr
 MILLER, E S 741*
 MILLER, R. E 150*
 MINOT, G R 563*
 MOORE, F D 214 - cr
 MUNRO, D 45 223*
 MURRAY, C R 265*
 MURRAY, R 611*, 701, 748 - mp
 MYERS, J D 737*
 MYERSON, A 301 - c, 821*

N

NEWELL, J L 851*

O

OLANSKY, S 817*
 ORY, E M 862*

P

PAINE, T F 611*, 701, 748 - mp
 PALMER, R S 874 - cr
 PATZ, A 697*
 PAUL, O 877 - cr
 PEET, M M. 270 - mms
 PERKINS, G E. 277*
 PICKLES, W 858*
 POLAND, O S 883 - c
 POPKIN, R J 337 - c
 PROVENZANO, R W 360*

R

RICHARDSON, W 292, 909 - cr
 ROBBINS, L L 38, 181 - cr
 ROBERT, W H 505*
 ROGERS, W F, JR 737*
 ROOT, H F 397*
 ROPES, M W 75 - cr
 ROSE, A S 109, 487 - cr
 ROSS, S 817*

ROTMAN-KAVLA, G 314*
 RUBENSTEIN, A D 87, 862*
 RUSSELL, G G 505*
 RYDER, C M 132 - mms

S

SAUNDERS, P 526*
 SCHALL, L 672 - cr
 SCHATZKI, R 148, 368, 407 - cr, 419 -
 mms, 481 - cr
 SCHEIDELL, D K 940*
 SCHIER, W W 898*
 SCHULTZ, P E 526*
 SCHULZ, M D 877 - cr
 SEGAL, M S 132 - mms
 SEIBEL, R E 683*
 SHORT, C L 78 - cr, 383, 429, 468*,
 670 - cr
 SIMMONS, C C 513 - cr
 SIMMONS, F A 601 - cr
 SMITH, G G 713 - cr
 SMITHWICK, R H 662 - mp, 851*
 SNIFFEN, R C 951 - cr
 SOBEL, E H 783*
 SOSMAN, M C 145, 330 - cr
 SPENCE, H M 13*
 SPIER, J 824*

SPRAGUE, H B 481 - cr
 STARE, F J 26, 68 - mp
 STEVENS, N C 552, 769 - c
 STUART, H C 507, 537 - mp
 STURGIS, S H 601 - cr
 SULLIVAN, C L 65*
 SWEET, R H 179, 672, 951, 955 - cr
 SWENSON, O 236*
 SWINTON, N W 169 - mms

T

TALBOT, N B 783*
 TAYLOR, F H L 351*
 TAYLOR, G W 207 - mp, 330, 515,
 909 - cr
 TAYLOR, I 109 - cr
 TENNEY, B, JR 102 - mp
 THOMA, K H 330 - cr
 THOMPSON, F G, JR 13*
 TICHY, F 729*
 TROLAND, C 419 - mms
 TURNER, N C 188 - c

V

VANDER LAAN, W P 236*
 VONDERLEHR, R A 996 - c

W

WANGENSTEEN, O H 121, 191 -
 WARREN, L O, JR 24*
 WATKINS, A L 799 - mp
 WATSON, R J 622*
 WAUD, S P 63*
 WELCH, C E 634 - cr
 WELCH, M L 95*
 WESSELHOEFT, C 943, 978 - mp
 WEST, W J 694*
 WHARTON, H J 974*
 WHEATLEY, G M 305*
 WHIPPLE, R A 239*
 WHITE, J C 989 - cr
 WHITE, P D 481 - cr
 WHITELAW, G P 962 - c
 WIGGIN, S C 526*
 WILLIAMS, C 443 - cr
 WILLIAMS, P A 727 - c
 WILLIAMS, R H 737*
 WILLIAMS, V P 322 - mp
 WILSON, N J 515 - cr
 WOOD, E G 824*

Y

YOUNG, R H 794*
 YOUNGE, P A 835 - cr

The New England Journal of Medicine

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Volume 236

JANUARY 2, 1947

Number 1

COARCTATION OF THE AORTA

A Review and a Report of a Case

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DETROIT, MICHIGAN

IN 1933 Sir Thomas Lewis¹ expressed the following opinion: "So much has been written about coarctation of the aorta that new records of cases can have little value unless they reveal new features of interest and importance to the study of the condition." With this sentence he began a paper that—for completeness in both theoretical and practical considerations, as well as in the presentation of the anatomic, physiologic and clinical features—can well be used as a model by present day authors on any medical subject.

The purpose of this paper is to report a case of coarctation of the aorta in a bombardier, to re-emphasize much of what Sir Thomas Lewis had to say about the subject, to abstract several points brought out by a few of the earlier and later writers, to exhort physicians to search for the condition oftener, to discuss the prognosis in coarctation of the aorta, particularly as the problem pertains to civil, military and Veterans Administration practice and, what is perhaps most important, to report on the recent advances in the surgical treatment of aortic atresia.

ANATOMY

Coarctation of the aorta is generally classified into two anatomic groups, both of which are located preponderantly in the distal portions of the arch. The first form, which is generally known as the infantile type, is characterized by a generalized narrowing of the arch in its distal portion, extending from the origin of the left subclavian artery to the region of insertion of the ductus arteriosus. Clinically, this form is rare, accounting for 7 of 183 cases cited in one series,² and is so frequently accompanied by other major developmental anomalies, such as a bilocular or trilocular heart, a transposition of the arterial trunks and pulmonary atresia,³ that death occurs in infancy. The adult type is characterized by an abrupt narrowing—

sometimes to the extent of obliteration—of the aorta in the proximity of the insertion of the ligamentum arteriosum (Fig 1), it should not be classed as a rarity in clinical medicine. Blackford⁴ found an incidence of 44 cases in 68,300 cases at autopsy (1 1550) reported by various observers. The incidence is 3 1 in favor of men. That the patient with the adult type of coarctation lives—and, in fact, may physically prosper—for years in spite of so marked a defect is probably due to the responsiveness of other vessels in forming a collateral circulation, as well as to the fact that the associated developmental anomalies, if any, are less serious than those found in the infantile group. These defects, which are comparatively minor,² fall into two main groups. The first comprises anomalies of the heart and great vessels, including bicuspid aortic valve, anomalous origin of the arteries of the aortic arch, persistent left superior vena cava, aortic septal defects and subaortic stenosis, and the second, anomalies of the body at large, including hypospadias, absence of the left kidney, vertical position of the stomach, horseshoe kidney, diaphragmatic hernia, subluxation of the joints, slight Mongolianism, ichthyosis, pigeon breast and congenital cerebral-vessel aneurysm. Because of the obvious value of a search for these associated anomalies these lists are taken directly from an article by Hamilton and Abbott.² These authors state that the defects of the heart and great vessels are so frequent as to be almost a part of the complex. Bauer and Iverson⁴ described a case accompanied by complete double pelvis and ureter and an accessory renal artery on the left. That many developmental anomalies exist in aortic coarctation may be fully expected with a defect that is probably an embryologic deviation itself.

PHYSIOLOGIC CIRCULATORY CHANGES

Marked anatomic changes of the various branches of the aorta, all designed to establish a satisfactory circulation to the organs normally supplied by

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arteries branching from the aorta distal to the coarctation, develop with the demands of the body. The formation of this collateral circulation,² although not uniform, takes place mainly through the

intrascapular and subscapular arteries, all of which arise from branches of the aortic arch and thus proximal to the stenosis, and the second intercostal artery, blood passes through the internal mammary

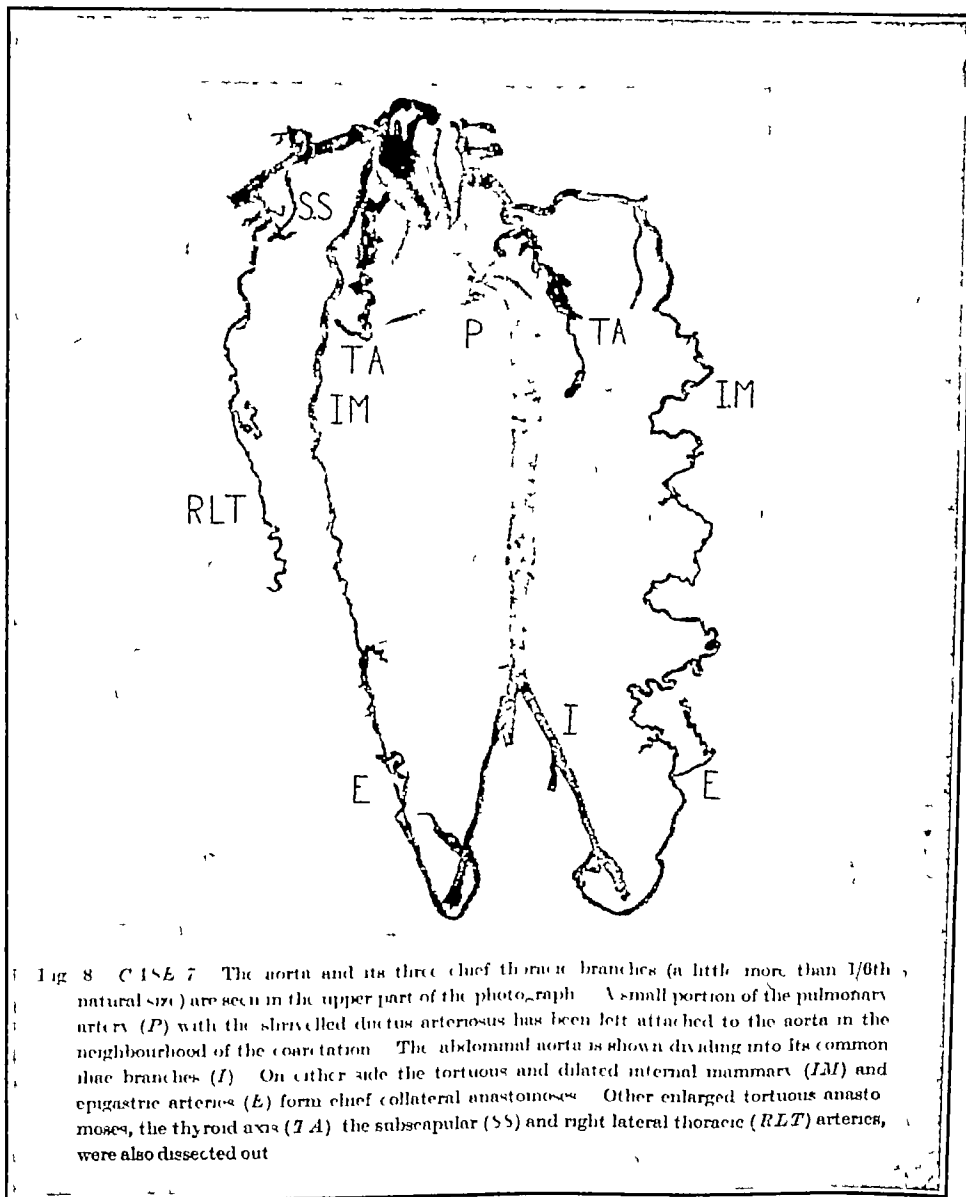


FIGURE 1

This illustration, taken from Lewis,¹ illustrates the formation of the collateral circulation.

following developments: an anastomosis between the superior intercostal artery, arising from the subclavian, and the first aortic intercostal artery, which comes from a point just distal to the stenosis; an anastomosis between the posterior scapular,

branch of the subclavian to the descending aorta via the epigastric and iliac arteries (Fig 1). This collateral circulation, when well developed, supplies sufficient blood to the aorta distal to the coarctation so that, even should obliteration be complete, cir-

culuation of blood to the viscera of the abdomen and to the musculature of the lower extremities is frequently satisfactory. It has been shown that the blood vessels of the skin and muscles of the lower extremities are normal in comparison to those of the upper extremities and regions supplied by blood vessels proximal to the coarctation.⁵

The blood flow appears not to be uniformly affected, since some authors have discovered a

nocturnal cramps in the legs of 2 patients over forty years of age, and they concluded that the velocity flow in the larger arteries of the legs was reduced and the femoral pulse delayed as much as 0.15 second after the radial pulse. They found the blood oxygen in the lower extremities not diminished in a patient at rest. Stewart and Bailey⁹ found the arm-to-perineum and arm-to-leg circulation times prolonged in most of 14 cases. The aorta and all



FIGURE 2

A roentgenogram, taken from Lewis¹ illustrates sulcation of the inferior borders of the posterior portions of the ribs

decrease in renal flow⁶ and others an increase in the peripheral vessels.⁷ In a careful study of 12 cases by Stewart and his associates,⁷ the circulation time was found to be prolonged in some, normal in a few and decreased in others. They point out that the prolongation of the circulation time was effected by the devious collateral routes of the blood and that the normal or decreased times were produced by a well developed increase in the cardiac output that overcame this handicap, the skin and rectal temperatures were also increased as a rule. Blumgart et al.⁸ noted intermittent claudication and

the arteries arising from it proximal to the constriction undergo absolute dilatation,* and the left ventricle usually hypertrophies slightly, especially if high blood pressure be present, in well marked, uncomplicated cases of coarctation. Lewis¹ believed that this dilatation produced a volume in the arterial bed proximal to the coarctated region about equal to the arterial volume in the normal person without

*Measurement of the degree of dilatation of the aortic branches would be tedious and technically difficult. To measure merely the mouths of the great branches at the aorta as suggested by some⁴ is entirely inadequate for the elasticity and the caliber of the lumen along the entire course of these vessels must be calculated to ascertain the complete degree of dilatation.¹

stenosis, in other words, the increased resistance to the blood leaving the left ventricle, expected on the contraction of that organ because of aortic constriction, is compensated for by dilatation of the proximal aorta and its branches. This answers part of the query of why a heart working against an increased tension is often little enlarged but leaves unanswered the question of the cause of the hypertension.

In view of one of the modern concepts of the etiology of hypertension, reduced blood flow to the

diastolic pressure in the femoral artery was almost the same as that in the brachial artery. This suggested that the peripheral resistance is increased in the legs as well as in the arms.

EMBRYOLOGY

Embryologists are probably quite close to the explanation of the development of coarctation of the adult type. Brunner¹¹ asserted that the tissue of the ductus arteriosus at its junction with the

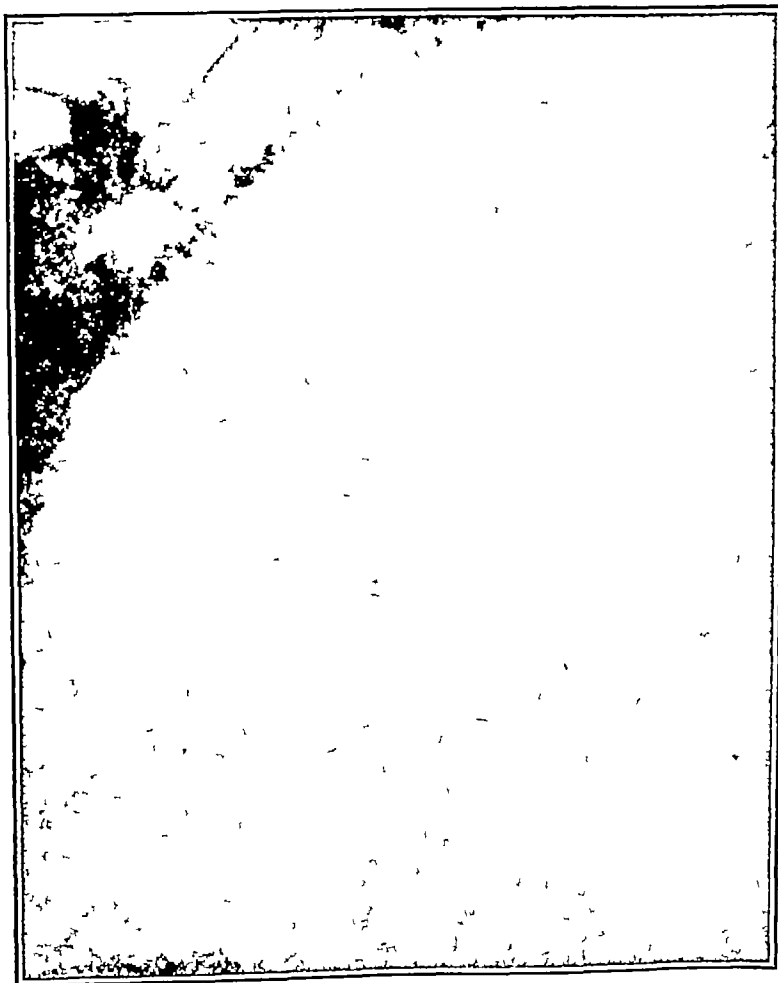


FIGURE 3

This roentgenogram, taken from Lewis,² is a left oblique view that illustrates the extension of the great-vessel silhouette high into the neck and an area of abnormal clearness posterior to the aortic column.

kidney, it is emphasized that the volume flow and circulation time to this organ may or may not be normal, although some believe that adverse changes have been demonstrated.⁶ Using direct puncture methods for determining the blood pressures in the brachial and femoral arteries in a case of coarctation, Steele and Cohn¹⁰ found that the systolic pressure in the brachial artery was higher but that the

aorta, which at birth naturally becomes completely stenosed, anomalously incorporates the contiguous portion of the aorta in this obliterating action. The primitive fourth arch (the aorta) falls prey to the obliterating overaction of the primitive sixth arch (the ductus). Some authors point out that the ligamentum arteriosum exerts a tent-rope-like tugging on the aorta at the junction of the two, causing

a kinking of the aorta that produces a stenosis. Just what the process is in the extremely rare cases of coarctation situated away from the region of the ductus insertion is difficult to conjecture. One case is cited in which the stenosis occurred proximal to the origin of the left subclavian artery,² and record has been made of a stenosis in the abdominal aorta.¹² Such locations lend support to the theory of Reynaud and Rokitsansky, who believed that coarctation

conspicuous by their absence. This is especially true, in the majority of cases, in the early decades of life — that is, until the reserve of nature's bounty is consumed. Patients rarely present complaints until early adulthood and usually reach the third and fourth decades before consulting a physician, in spite of the fact that the expectancy of life is much shortened. Abbott¹³ reported that in 74 per cent of 200 cases the patients died during or before



FIGURE 4

A roentgenogram, taken from Lewis,¹ showing the area of abnormal "clearness" posterior to the aortic column in the right oblique view

was due to embryonic maldevelopment of the descending limbs of the primitive left aorta

SYMPTOMS

Although the adult type of coarctation of the aorta is present at or soon after birth (if Skoda's theory of postnatal paulocardia is correct) and persists throughout life, — whose span it definitely shortens as pointed out below, — the symptoms are

the fortieth year. Lewis's¹ report included 8 soldiers, all of whom had led vigorous lives in childhood and who had done well during rigorous training or combat in World War I. One of his patients first presenting symptoms of fatigability and breathlessness on exertion at the age of nineteen years had, in boyhood, walked several miles each day to school, performed physical drill and played with his school fellows such games as cricket, football and leapfrog

without difficulty, after returning home he had played in the streets till late, going to bed at 10 or 11 o'clock. He had frequently taken part in races of several miles' length and had held his own. For five years he had worked with a cabinetmaker, doing heavy carpentering and portering for twelve hours a day, he had played football on Saturday afternoons and had usually walked six miles on Sundays. After three months of full military training at the age of nineteen, the patient had first noticed breathlessness and palpitation on exertion, in addition to an occasional cough and frequent giddiness. He was discharged from the Army at that time because of heart disease, but two years later he was again passed as healthy and returned to training, after which the symptoms recurred. From then on, with the history of continual reappearance of symptoms when he attempted heavy physical activity, the course was downward. At the age of thirty-one, he collapsed suddenly and died on his way to the hospital. A second soldier, who had passed his physical examination at the age of forty-six and had campaigned without symptoms in France and Macedonia for three and a half years, after contracting malaria, had developed breathlessness on effort, pain across the chest anteriorly, fatigability, giddiness and frontal headaches, semi-invalided at the age of sixty-three, he was still under treatment at the time of the report. These cases, with 6 others cited, demonstrated typical histories of early well-being, with symptoms of breathlessness and palpitation on exertion, chest pain, giddiness and cough first ushered in at an adult age by some extraordinary incident such as extreme exertion or infection. Frequently, once the symptoms have made their appearance, invalidism develops and death from cardiovascular failure ensues. In Lewis's 9 cases, 2 patients began to have symptoms as early as nineteen years of age, 1 at twenty-seven, 1 at thirty-three, 1 at forty, 1 at forty-one and 2 at forty-eight. The significant chronologic data in these cases are presented in Table 1. Death has occurred early in childhood and as late as ninety-two years of age, as in Reynaud's case, quoted by many writers.

The important symptoms, beginning after years of apparent good health, consist mainly of breathlessness and palpitation on exertion, fatigability, slight cough, sometimes giddiness with hot flushing of the face, headaches and thoracic pain. The period of latency is strongly emphasized by Abbott.¹⁸ The patient in the case reported below was referred by a neuropsychiatrist to whom he had been sent because of nervousness, precordial pain and palpitation were also present in slight degree.

PHYSICAL SIGNS

No disease—certainly no congenital cardiovascular disease—furnishes such unmistakable physical signs as coarctation. Foremost of all find-

ings is the reversed relation of the brachial and popliteal arterial blood pressures. The ordinary increase in pressure from 10 to 50 mm of mercury at the popliteal artery is not present, and the pressure in the brachial artery is usually abnormally high, whereas the popliteal pressure is actually considerably lower.¹⁴ The femoral pulsation is weaker, with a definite lag in its summation, and compared to the radial pulse it is slightly delayed in its travel following ventricular systole. In my opinion, comparison of the pressures in the brachial and popliteal arteries is the *sine qua non* of diagnosis, although

TABLE 1 Important Chronologic Data in Cases of Coarctation Reported by Sir Thomas Lewis¹

CASE No	AGE AT ONSET OF SYMPTOMS	AGE AT DIAGNOSIS	AGE DURING INVALIDISM	REMARKS*
1	19	24	29-31	Sudden death at age of thirty-one
2	49½	50	50-	Patient still alive at age of sixty three
3	19	35	19-	Patient still alive at age of thirty seven
4	40	46	40-52	Death from congestive failure at age of fifty two
5	49	58	50-61	Death from pneumonia at age of sixty-one
6	27	33	40-41	Sudden death at age of forty-one
7	33	42	42-43	Death from congestive failure at age of forty-three
8	41	49	41-49	Sudden death at age of forty nine
9	68	—	—	Patient brought in dead with no history available diagnosis made at autopsy

*Much of the lag in years between the onset of symptoms and the date of diagnosis took place while the patients were under close medical study. Some were cases in Sir Thomas's own clinic. Case 3 had been seen more than once by Sir William Osler and Sir James Mackenzie neither of whom had made the diagnosis.

Lewis¹ stresses inspection of the neck and thorax for enlarged arteries engaged in the collateral circulation. It may be argued that any physician can take blood pressures,* whereas many physicians, particularly in this age of gadgets, are poor observers. Although a brachial arterial hypertension for both systolic and diastolic values is the rule, the brachial pressure is occasionally normal.¹⁴ Bauer and Iverson⁴ encountered difficulty in the diagnosis of their 2 cases of moderate coarctation without signs of collateral circulation. In 1, the arterial pressure in the upper extremity was 30 mm of mercury higher than that in the lower (the key to the diagnosis), and in the other no comparison of the two pressures was made. Both patients were in the throes of cardiovascular decompensation—a condition in which it is unreasonable to expect invariably large, pulsating collateral vessels in the neck and trunk, even if collateral vessels, which do not always form and which at autopsy in these cases were absent, are developed, the reversal of the normal relation of

*The usual blood pressure cuff in use at present is not well designed for recording pressures in the thigh, snug fitting of the cuff being difficult, especially in obese patients. Manufacturers should produce a larger cuff for this purpose.

brachial and popliteal arterial tensions, on the other hand, still pertains

Many other signs that are neither so frequently found nor so nearly pathognomonic include the following: left ventricular enlargement, a systolic murmur precordially and along the routes of enlarged collateral arteries such as the intercostal and the internal mammary arteries, diminished or absent pulsation of the arteries of the lower extremities, capillary pulsations in the face, increased pulsation in the episternal notch, and a tendency to a water-hammer quality of the radial pulses. Perlman¹⁵ states that 9 of 13 patients had a basal dias-

bilaterally, first described by Meckel¹⁶ in 1827 and emphasized by Railsback and Dock¹⁷ in 1929 and by others^{11, 15} (see Figs 2, 5 and 6). This phenomenon, which is found particularly in cases of long standing, is undoubtedly due to rib erosion by the forceful pulsations of the enlarged intercostal arteries. Secondly, one might expect to see variations in the silhouette of the great vessels in the upper mediastinum. Sir Thomas Lewis's description of the x-ray appearance is as follows:

The features of the x-ray silhouette in coarctation that seem to be sufficiently constant to be regarded as significant are two in number. Firstly, there is the increased

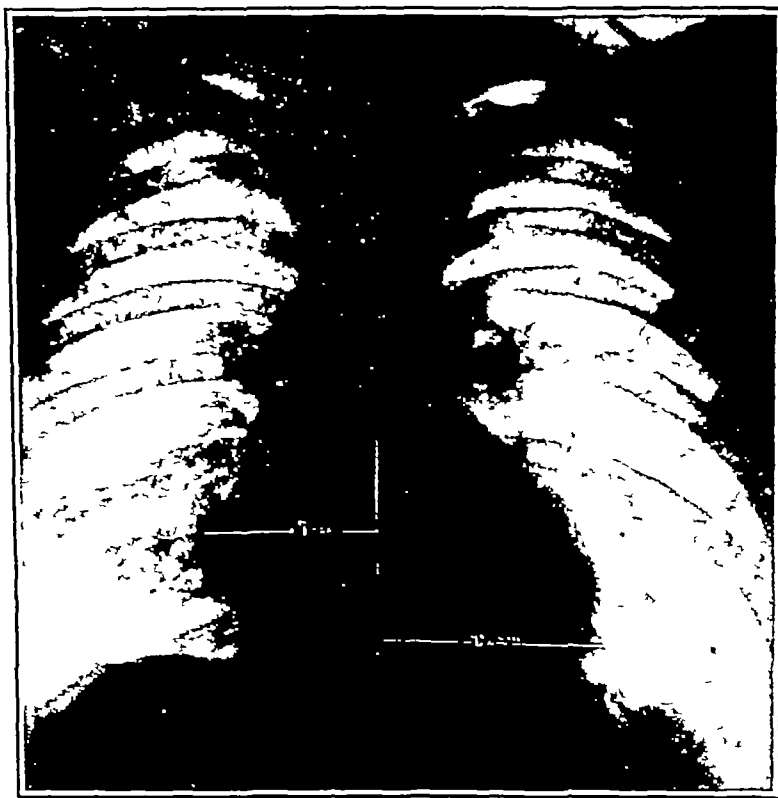


FIGURE 5

This roentgenogram shows loss of the expected prominence of the aortic knob. Sulcation of the ribs is barely visible.

tolic murmur, 1 had a precordial systolic murmur and 3 had no cardiac murmur.

X-RAY FINDINGS

A roentgenogram of the thorax usually furnishes strong aids in the diagnosis of coarctation. The first and rather pathognomonic* finding is the scalloping of the inferior borders of the posterior ribs.

*Rarely, other pathologic conditions may cause scalloping of the rib borders. Dr. Edwin M. Wright, of the Department of Roentgenology, University of Michigan, has recently shown me sulcation of the ribs in the x-ray film of a patient suffering from neurofibromatosis. It is conceivable that other types of neoplasm may cause somewhat similar changes.

breadth and density of the shadows of the basal vessels, this is associated with their dilatation but it is not characteristic of coarctation in that it also occurs in cases of simple high tension. Secondly, there is the inability to trace out the aortic arch, a fact particularly significant when it applies to the left oblique position. It is the more noteworthy because a normally developed aorta under the strain of high internal pressure is wide and throws a dense shadow, which can usually be distinguished with ease, even after it passes into the shadow of the vertebral column. In coarctation, the aorta being untraceable, the aorta and its unusually prominent branches rise as a conspicuous column from the heart, high into the thorax and root of the neck. Behind this column at its base there is an area of abnormal clearness opposite the bodies of the 6th, 7th and 8th dorsal vertebrae.

Figures 3 and 4, taken from Lewis, and Figures 6 and 7, which demonstrate the findings in the case presented below, are illustrative. Some eager scientists prefer a more definite delineation of the great vessels by the injection of a contrast medium, such as Diodrast, into the circulation. Careful studies of this type have been reported by Blumenthal and Davis¹⁸ and by Grishman, Steinberg and Sussman,¹⁹

combined, are as pathognomonic as any signs in the science of diagnosis: a decrease of the arterial pressure in the lower extremities, usually to a point below the brachial-artery tension, a small femoral pulsation the summit of whose upstroke lags behind that of the radial pulsation—a lag of 0.145 second according to accurate measurements by Sir Thomas Lewis, visual, palpable or auditory

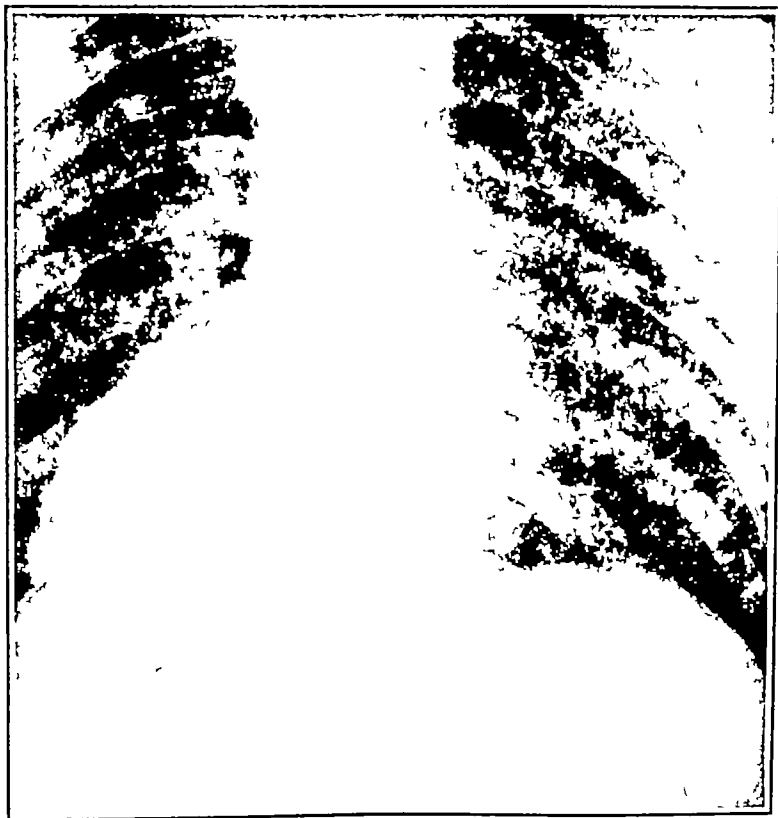


FIGURE 6

The posteroanterior view of the posterior ribs more clearly illustrates the sulcation of the ribs

and some consider the method the only available test for certain atypical forms of coarctation.²⁰

ELECTROCARDIOGRAPHIC FINDINGS

Except for indications of a left ventricular preponderance in cases with well marked arterial hypertension, the electrocardiograph is of little value in the study of coarctation. Patients showing right-axis deviation have been reported by Stalker,²¹ Moragues et al.,²² Schwartz and Greene²³ and Stewart et al.⁷ Auricular fibrillation might be expected in some patients undergoing myocardial failure,^{8, 20} and right bundle-branch block has been reported.⁸ Negativity and coving of T₁ occurred in 8 of 12 cases studied by Stewart et al.,⁷ and these changes often indicated a poor prognosis.⁹

In summary, it can be said that the following five findings in coarctation of the aorta, when com-

binations of increased pulsations of various arterial branches of the aorta, or a combination of two or more of these, sulcation along the inferior margin of the posterior portions of the ribs, and absence of the aortic knob and abnormal extension toward the neck of the silhouette of the supracardiac vessels

CASE REPORT

A 26-year-old bombardier, a veteran of sixty-five "rough" missions over Germany and France during the 10 months beginning in April, 1944, noticed sharp fleeting pains across the center of the precordium in October, of that year. These pains occurred only during rest, and although palpitation and moderate breathlessness were noticed after physical exertion, there was no associated apprehension. The patient was aware of a steadily increasing incidence of the pains, as well as of a growing nervousness, but he considered both to be due to the fact that he was "crowding in as many missions as possible in order to get it over." On returning to the United States, the patient was found to have a heart murmur with high blood pressure, because of which he was removed from flying status. His current duties in the Army were light, but he continued to have precordial pains (as

many as twenty fleeting attacks a day), slight breathlessness on exertion and indefinite nervousness with irritability. During the preceding few months he had occasionally had brief spells of giddiness. Close questioning revealed no history of cough, hemoptysis, edema, cyanosis, flushing of the face, tingling or coldness of the lower extremities or indigestion. Until the onset of the present illness the patient had always been unusually strong and well.

In the family history it was stated that his father, at the age of 63, had chronic rheumatism, a brother had had inflammatory rheumatism, and another had had a questionable

to the left of the 6th and 7th thoracic vertebrae and along the course of the right 4th and 5th ribs posteriorly. The postmanubrial and precordial dullnesses were normal. A moderate (Grade II or III), fairly high-pitched, late systolic murmur was heard over the precordial 3rd and 4th interspaces and along the left border of the sternum. No diastolic murmur was detected. On exercise the murmurs along the right intercostal spaces became louder, whereas the murmur described in the left scapular region became inaudible when the patient stood erect but returned when he assumed a stooping position — a surprising phenomenon that occurred



FIGURE 7

This roentgenogram shows the clear area in the retrocardiac space in the right oblique view

chorea. Perhaps relevant to the patient's condition was the fact that his mother had suffered from high blood pressure and kidney disease for years before a terminal right hemiplegia at the age of 50.*

Physical examination in April, 1945, disclosed a symmetrically developed man, 72 inches in height and 180 pounds in weight. He appeared to be especially rugged, with no apparent discomfort or pain. When a tension of 160/90 in the left and 158/80 in the right brachial arteries was observed, the right and left popliteal pressures were taken and found to be 98/78 and 98/85 respectively. No pulsations could be seen or felt over the thoracic or abdominal surfaces, but a soft rather high-pitched murmur was distinctly heard just

after some episodes of the exercise (fifty hops on each foot) but not others.† That the patient's arterial bed was elastic is demonstrated by the blood-pressure changes following exercise, the brachial-artery tension varying from 110/90 to 160/80 and the popliteal tension from 98/78 to 105/75. The femoral pulses felt weak, and the dorsalis pedis and posterior tibial arteries were not palpable at any examination.

The urine was normal and serologic tests were negative. The electrocardiogram (Figs 8 and 9) was entirely normal with no evidence of axis deviation. The roentgenograms (Figs

*I am not aware of any studies pertaining to possible familial aspects of coarctation except for a report of cases in a father and son, symptoms beginning in the former at the age of thirty-four and in the latter at the age of fifteen.²⁴

†The systolic murmur at the coarctation is probably formed by the rush of blood from the narrow constricted passage into the larger spindle immediately distal. Perhaps the murmur was not produced in the upright position after exercise because of the increased volume of blood reaching the lower aorta through the collateral arteries, keeping the sides on either side of the stenosis "too full for sound and foam." On stooping over the volume flow may have been impeded enough to allow the production of a murmur.

6 and 7) exhibited absence of the aortic knob in the anterior view and increased height of the great supracardiac vessels in the oblique projections, although the left oblique view was not considered satisfactory.

The patient was given a medical discharge from the Army at the time the diagnosis was first made, 7 months after the onset of symptoms. Five months later he reported that he was having many headaches and an increased fatigability. He found it difficult to do his former work.

COURSE AND PROGNOSIS

Sir Thomas Lewis¹ struck a hopeful note in the prognosis of coarctation, probably because the anomaly can be present long before the appearance of symptoms. It is significant, however, that 6 of the 8 patients he had seen during life were dead

are alive and well whose cases were not reported in the literature, and there are many sufferers with undiagnosed cases, coarctation, however, is a disease of high morbidity and low longevity when once it has become symptomatic. Sooner or later, some episode of infection or unusual physical strain results in successive circulatory evils, and arteritis, aneurysms, bacterial vascular infections, myocarditis and embolization cause cardiovascular reserve to flutter, a fatal outcome subsequently follows.

COMPLICATIONS

The complications, all of which are cardiovascular, have been discussed above. It is interest-

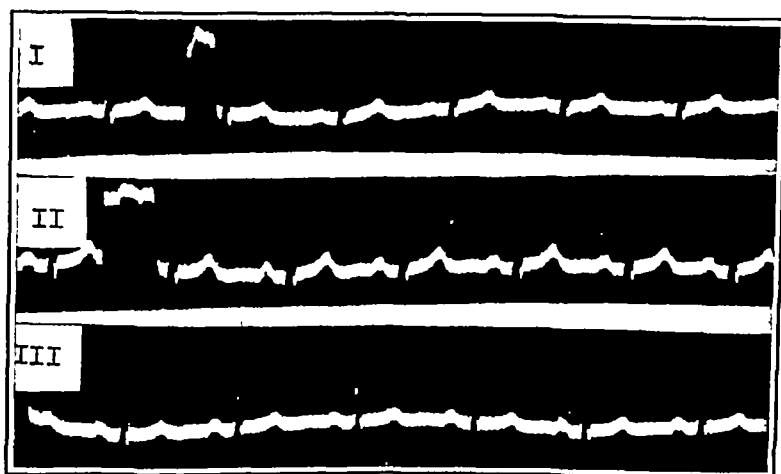


FIGURE 8 *Electrocardiogram — Limb Leads*

at the age of fifty-two, with the exception of 1 who died from pneumonia at the age of sixty-one. Two patients, thirty-seven and sixty-three years of age, were alive at the time of the report. All were symptomatic. Abbott¹³ reported 128 fatal cases before the age of forty in her 200 collected cases, the main causes of death being failure of the myocardium, rupture of the aorta, mycotic endarteritis and aneurysm, frequently with an associated glomerulonephritis, and cerebral hemorrhage, probably based on congenital aneurysm of the cerebral arteries. Many observers have reported rupture of the aorta, in 1 case the rupture occurred 1 cm. distal to the aortic cusps, with emptying into the pericardium,²⁶ and another caused a dissecting aneurysm of the aortic arch.²⁶ Moragues et al.²² cited 5 cases of rupture of the aorta distal to the atresia and reported a case of their own in which the aorta just below the coarctation had ruptured into the esophagus, causing hematemesis. Goodson²⁷ published a case in which the distal aorta ruptured into a bronchus, causing hemoptysis. It is difficult, at present, to be anything but pessimistic in the prognosis of coarctation of the aorta. Of course, many patients

ing to note that only 1 patient is reported to have died from Bright's disease²⁸ — a further indication of an undisturbed blood supply to the kidneys.

TREATMENT

A simple regime of rest, both physical and mental, was the only indicated therapy until recently. If emphasis is placed on the early diagnosis of coarctation, especially before the appearance of symptoms, this form of therapy will doubtless add years to the patient's life. It behooves every examiner to keep the possibility in mind, especially in any case of arterial hypertension. A diligent examination and reappraisal of all cases of high blood pressure may prove most enlightening to the physician. Lewis,¹ investigating the effects of vasodilators on about 30 hypertensive patients in his outpatient department, discovered 5 of the 9 cases he reported. It is not too much to hope that early diagnosis and the early institution of rest, or at least protection against infections and excessive mental and physical rigors, may postpone invalidism and prolong life. Foci of infection should be carefully eliminated.

Those who discover hypertension and other cardiovascular anomalies in children may become particularly helpful in the diagnosis and treatment of coarctation of the aorta. Blumenthal and Davis¹⁵ report the defect in a twelve-year-old child and in a twenty-month-old infant, the latter showing a blood

Greene²³ reported 2 cases in children — a girl of eight and a boy of nine years of age — in whom the atresia also involved the left subclavian artery so that pulsations were absent in the left arm as well as in both lower extremities. Both had an asymmetry of the upper body with a larger face, thorax

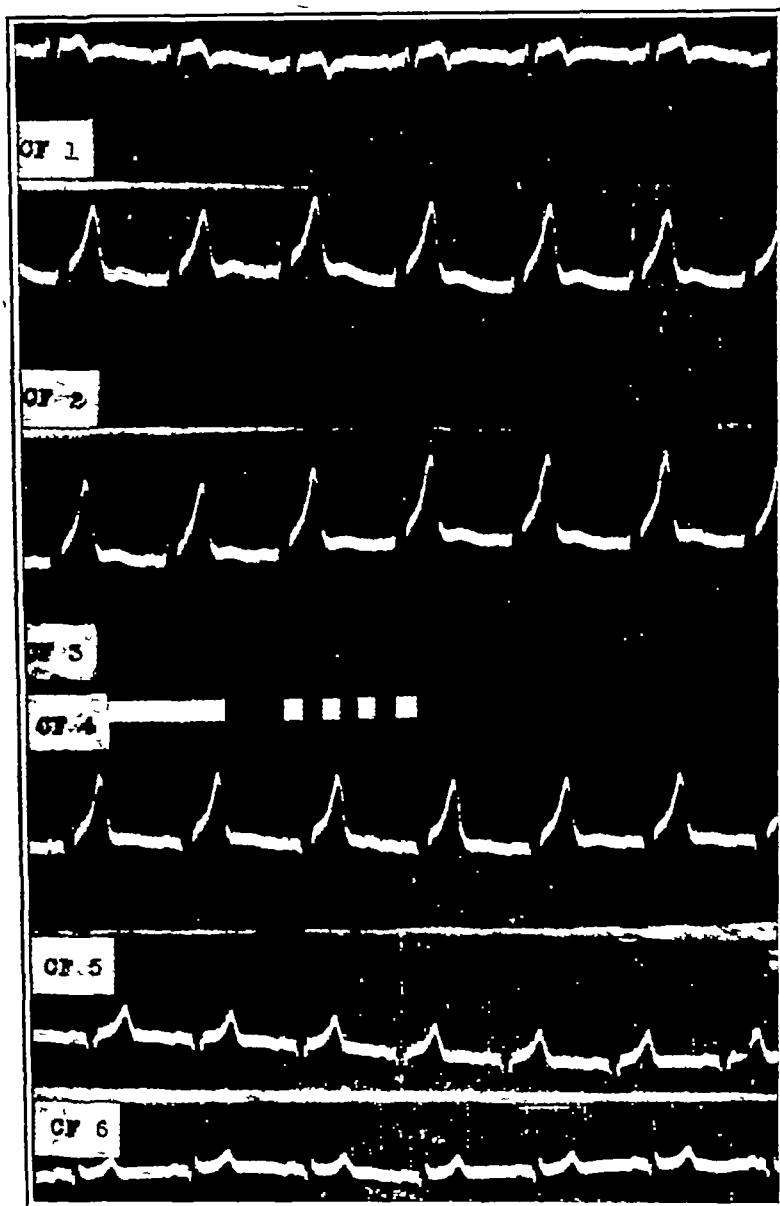


FIGURE 9 *Electrocardiogram — Precordial Leads*

pressure of 170 systolic, 110 diastolic, in the upper extremities but no recording being possible in the lower, in the former, a contrast medium of Diodrast was helpful in demonstrating the atresia at the insertion of the ligamentum arteriosum, as well as a dilated internal mammary artery. Schwartz and

and arm on the right. The boy, who had a widely patent ductus arteriosus, exhibited no rib erosion, whereas the girl had erosion of the ribs on the right side only. The authors point out that superficial collateral circulation is rare in children. Eisenberg²⁹ found the diagnosis of aortic coarctation in chil-

dren to be increasing. He added 3 cases in children to the literature. In 1 case the lower extremities were definitely cold to the touch, whereas in another patient, a nine-year-old child, there were a flushed face and intermittent claudication. These authors are cited to emphasize the relative frequency of the defect so that physicians may develop an awareness of it and take steps for treatment before it is too late. The remarkable advances made by the surgeon in the handling of the great blood vessels offer hope. Blalock³⁰ has done much to place this type of surgery on a firm foundation, and Gross and Hufnagel³¹ have already cured coarctation of the aorta anatomically and clinically in a twelve-year-old child. Gross³² reports that they have performed operations in a total of 12 cases, with success in 10. The reports of these authors should be read by all physicians, for no one can help marveling at their courage and expert technic. The surgeon may well have a cure for coarctation.

DIFFERENTIAL DIAGNOSIS

There is nothing typical about the patient's complaints in coarctation of the aorta. Any number of cardiovascular diseases produce the same symptoms. The signs, however, are definite and, when present in combination, are pathognomonic. The findings of a high arterial tension, with a reversal in the relation of the pressures in the brachial and popliteal arteries, and signs of a collateral circulation in the vessels of the thorax and a lag in the summation of the femoral pulse are usually distinctive and should serve to make the physician wary of the diagnosis of other forms of hypertension. The prominence of the aortic knob seen in essential hypertension is usually absent in coarctation. The x-ray film often exhibits a moderate dilatation of the ascending aorta in the uncomplicated case of coarctation, but no aneurysmal enlargement is seen. The silhouette of the dilated supracardiac vessels rises high toward the neck. If complications, such as congestive failure, aneurysms, bacterial vascular infections and embolic phenomena, occur, the picture may be confused. But the changes in the relative arterial tension, the lag of the femoral pulse summit and the x-ray findings—in the great vessels, scalloping of the ribs—should be elucidative in such cases.

* * *

Since the first case report of coarctation of the aorta by Paris³³ in 1791, the anomaly has attracted the attention of many great physicians—for example, Sir Ashley Cooper (1818), Meckel (1824), Laennec (1826), Reynaud (1828), Rokitsansky (1848), Barie (1886), MacCallum (1900), Minkowski (1901), Libman (1902), Pappenheimer (1905), Mönckeberg (1907), Abbott (1928) and Sir Thomas Lewis (1933). The defect is embryologic and occurs at all ages. The symptoms, which usually do not appear before adult life, are similar to those in many

types of cardiovascular failure and are not distinctive. When they once appear, the outlook is usually not bright and various degrees of invalidism are the rule. The span of life is shortened, cardiovascular complications of various types being the almost universal cause of death. The signs are definite and, when exhibited in combinations of two or three positive findings, pathognomonic. One can be sure that the defect is not rare. It has been said that coarctation occurs in about 0.10 per cent of the entire population.³⁴ In a routine examination of men between the ages of eighteen and thirty-five for military services, the known incidence was approximately 1 in 10,000.¹⁵ In a large army general hospital, 113 of 2685 patients studied on the medical service had hypertension, and 39.7 per cent of these were under thirty years of age.³⁵ A search through such fields as this, including the Veterans Administration Medical Service, is bound to uncover more cases of coarctation. Since, more than ever before, cure of this disease can be hoped for, every diagnostician should make a search for it. The diagnosis is easy and interesting. Perhaps it is not too much to hope that the surgeons will be able to cure many of the patients with this disease in the not too distant future.

REFERENCES

1. Lewis, T. Maternal relating to coarctation of aorta of adult type. *Heart* 16:205-243, 1933.
2. Hamilton, W. F. and Abbott, M. E. Coarctation of aorta of adult type. I. Complete obliteration of descending arch at insertion of ductus in boy of fourteen. bicuspid aortic valve. Impending rupture of aorta. cerebral death. II. Statistical study and historical retrospect of 200 recorded cases with autopsy, of stenosis or obliteration of descending arch in subjects above age of two years. *Am Heart J* 3:381-421, 1928.
3. Blackford, L. M. Coarctation of aorta. *Arch Int Med* 41:702-735, 1928.
4. Bauer, D. de F., and Iverson, L. Coarctation of aorta: report of two cases relating clinical data to degree of constriction measured at autopsy with method of standardization for related measurements. *Am Heart J* 30:30-38, 1945.
5. Graybiel, A., Allen, A. W., and White, P. D. Histological study of arterioles of muscle and skin from arm and leg in individuals with coarctation of aorta. *J Clin Investigation* 14:52-56, 1935.
6. Friedman, M., Selzer, A., and Rosenblum, H. Renal blood flow in coarctation of aorta. *J Clin Investigation* 20:107-111, 1941.
7. Stewart, H. J., Haskell, H. S., and Evans, W. F. Peripheral blood flow and other observations in coarctation of aorta. *Am Heart J* 28:217-232, 1944.
8. Blumgart, H. L., Lawrence, J. S., and Ernestine, A. C. Dynamics of circulation in coarctation (stenosis of isthmus) of aorta of adult type: relation to essential hypertension. *Arch Int Med* 47:806-823, 1931.
9. Stewart, H. J., and Bailey, R. L., Jr. Cardiac output and other measurements of circulation in coarctation of aorta. *J Clin Investigation* 20:145-152, 1941.
10. Steele, J. M., and Cohn, A. E. Nature of hypertension in coarctation of aorta. *J Clin Investigation* 17:514-1938.
11. Brunner, F. Ein Fall von Obliteration der Aorta an der Einmündungsstelle des Ductus Botalli. *Deutsche med Wchnschr* 24:794-798, 1898.
12. Maycock, W. d'A. Congenital stenosis of abdominal aorta. *Am Heart J* 13:633-646, 1937.
13. Abbott, M. E. Coarctation of aorta of adult type: statistical study, and historical retrospect of 200 recorded cases with autopsy, of stenosis or obliteration of descending arch in subjects above age of two years. *Am Heart J* 3:574-618, 1928.
14. King, J. T. Blood pressure in stenosis at isthmus (coarctation) of aorta: case reports. *Ann Int Med* 10:1802-1827, 1937.
15. Perlman, L. Coarctation of aorta: a clinical and roentgenologic analysis of thirteen cases. *Am Heart J* 28:24-38, 1944.
16. Meckel. Cited by Railsback and Dock W.
17. Railsback, O. C., and Dock, W. Erosion of ribs due to stenosis of isthmus (coarctation) of aorta. *Radiology* 12:58-61, 1929.
18. Blumenthal, S., and Davis, D. B. Coarctation of aorta in childhood: report of two cases in which diagnosis was confirmed by intra venous injection of diiodrast. *Am J Dis Child* 62:1224-1232, 1941.
19. Grishman, A., Steinberg, M. F., and Sussman, M. L. Contrast roentgen visualization of coarctation of aorta. *Am Heart J* 21:365-370, 1941.
20. Grishman, A., Sussman, M. L., and Steinberg, M. F. Atypical coarctation of aorta, with absence of left radial pulse. *Am Heart J* 27:217-234, 1944.
21. Stalker, H. J. Coarctation of aorta: case with right axis deviation of electrocardiogram and auricular fibrillation with some statistics. *J Michigan M Soc* 41:40-43, 1942.

- 22 Moragues V, Moore L T and Rosen, J A Coarctation of aorta with rupture of wall below point of constriction report of case and review of literature *Am Heart J* 24 828-834 1942
- 23 Schwartz, S P and Greene D Coarctation of aorta in children syndrome of constriction of isthmus of aorta with involvement of origin of left subclavian artery *Am Heart J* 23 99-115 1942
- 24 Walker W G Coarctation of aorta in father and son *New Eng J Med* 211 1192-1195 1934
- 25 Regester R P., and Innes M B Spontaneous rupture of aorta with hemopericardium caused by coarctation *Am. Heart J* 15 365-369 1938
- 26 Lewis R B Coarctation of aorta with congenital bicuspid aortic valve and dissecting aneurysm of arch of aorta *Am J Clin Path* 15 297-301, 1945
- 27 Goodson W H Jr Coarctation of aorta report of two unusual cases *New Eng J Med* 216 349-345 1937
- 28 Rosenstein Cited by Abbott 13
- 29 Eisenberg G Recognition of coarctation of aorta (adult type) during childhood *J Pediat* 13 303-308 1938
- 30 Blalock A and Park E A Surgical treatment of experimental coarctation (atresia) of aorta *Ann Surg* 119 445-458 1944
- 31 Gross R E, and Hufnagel C A Coarctation of aorta experimental studies regarding its surgical correction *New Eng J Med* 233 287-293 1945
- 32 Gross R E Personal communication
- 33 Paris M Cited by Abbott 13
- 34 Levine S Cited by Perlman 15
- 35 McFarland M D Hypertension in Army general hospital *M: Surgeon* 97 209-215 1945

HORMONE-PRODUCING TUMOR OF ADRENAL CORTEX, WITH CONGENITAL ABSENCE OF CONTRALATERAL ADRENAL GLAND

Report of a Case

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ALTHOUGH hyperfunctioning tumors of the adrenal cortex are rare, they are the subject of an increasing number of reports in the current literature owing both to improved diagnostic procedures, such as perirenal air insufflation and assay of the sex hormones excreted in the urine, and to increasing knowledge of the physiology of the adrenal cortex, especially in its interlocking relation with the function of the pituitary gland and the gonads.

The purpose of this communication is to present a case of a hormone-producing tumor of the adrenal cortex characterized by the symptomatology of Cushing's syndrome and associated with complete absence of the opposite adrenal gland. In addition the recent literature on such tumors is briefly reviewed. Grollman¹ presented an exhaustive review of the literature of adrenal physiology and pathology up to 1936.

CLASSIFICATION OF ADRENAL TUMORS

In classifying adrenal tumors it must be borne in mind that the human adrenal gland is actually two glands fused together in development in one enveloping capsule. The medullary portion is derived from the neural crest of the ectodermal germ layer, and tumors of the medulla are therefore classified according to the sympathetic-nervous-system cell type from which they originate into the following groups: sympathoblastoma (from the basic nerve cells), ganglioneuroma (from the cells of the sympathetic ganglion), and pheocytoma or paraganglioma (from the pheocytes). The first two types occur primarily in children, and the last occurs chiefly in adults and is characterized by hypertensive crises.

Tumors derived from the adrenal cortex, on the other hand, are mesodermal, glandular tumors that may be cytologically divided into hyperplasias,

adenomas and carcinomas. Cahill,²⁻⁵ who has written extensively on the subject, offers the following clinical classification: those with no recognizable hormonal changes, those with changes due to excess androgens that cause adult masculinity in the female child, masculinity in the female adult and adult masculinity in the male child, those with changes due to excess estrogens causing femininity in the adult male, those with changes due to excess androgens and other steroids and exemplified by Cushing's syndrome with associated sexual changes in the male and the female, and those with changes due to excess of other steroids related to metabolism which produce Cushing's syndrome without sexual changes in the male and the female.

The changes in the female child with a masculinizing tumor of the adrenal cortex have been described as pseudohermaphroditism. The first successful operation for a hormone-secreting adrenal tumor in a child was performed in a case of this type in an eighteen-month-old girl with virilizing symptoms reported by Collett⁶ in 1924. Several additional successful cases have been reported, as well as a number of deaths. It has been noted in the latter group that associated metabolic changes were usually present and that acute adrenal insufficiency was a factor in the fatal outcome.

The term "adrenocorticotrogenital syndrome" or "adrenal virilism" has been applied to the occurrence of masculinizing symptoms in adult women. This condition is characterized by hirsutism, amenorrhea, atrophy of the breasts, enlargement of the clitoris and male habitus. Cahill emphasizes that of several hundred cases of virilism investigated at his clinic, only a comparatively small proportion were found to have actual tumors of the adrenal cortex.

Masculinizing tumors in immature males are rare. They result in precocious puberty, with its associated bodily changes. The so-called "infant Hercules"

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type belongs in this category, although such cases have also been reported without adrenal tumors

Feminizing tumors in the adult male are also quite rare. Simpson and Joll⁷ reported the sixth such case in 1938. In their case excessive estrogenic substance, which had been excreted in the urine preoperatively, disappeared after successful operation and reappeared when metastatic recurrence became evident.

The group of cases with symptoms due to excess androgens and other steroids is exemplified by cases of Cushing's syndrome with associated sexual changes. This combination occurs principally in adult females, although an increasing number are being reported in children, and accounts for the largest number of tumors of the adrenal cortex, although it is not confined to tumor cases.

Cushing's syndrome without sexual changes, which is due to excess production of sterols related to metabolism alone, is discussed below.

It is thus seen that the clinical picture produced by a tumor of the adrenal cortex depends on the sex and age of the patient at onset and on the varying combinations of androgenic, estrogenic and metabolic hormones secreted. Cahill¹²⁻⁵ points out that the excess production of the metabolic hormones causes the functional or actual atrophy of the opposite gland. On the contrary, excess production of the androgenic hormones alone does not cause depression of the production of the life-maintaining substances by the opposite gland. This is of great importance in the prognosis following surgical extirpation of tumors of the adrenal cortex.

RELATION OF CUSHING'S SYNDROME TO ADRENOCORTICAL TUMORS

In 1932 Cushing⁸ described a syndrome, which has since borne his name, characterized by rapidly developing obesity confined to the face, neck and trunk (so-called "buffalo obesity"), plethora of the face, purplish striae over the lower abdomen and thighs, acne, amenorrhea and hirsutism in the female and impairment of sexual powers in the male. In addition, hypertension, frank or latent diabetes, disturbance of the nitrogenous metabolism and osteoporosis are frequently present. Furthermore, although not necessarily a part of the syndrome, virilism in women, as evidenced by masculine voice, atrophy of the breasts and hypertrophy of the clitoris, is often present. Cushing's syndrome occurs oftenest in adult women, next in frequency in children and less often in men.

Cushing attributed the syndrome to excessive secretion from a basophilic adenoma or hyperplasia of the basophilic cells of the anterior portion of the pituitary gland. Subsequently, as numerous cases of the syndrome appeared in the literature, it became apparent that the symptoms of many, if not a majority, were due not to primary pituitary disease but to hormone-secreting tumors of the adrenal

cortex, whereas in a few cases thymic tumors or arrhenoblastomas of the ovary were found to be the principal pathologic lesions. In a considerable number of autopsied cases of Cushing's syndrome no pituitary basophilism was found, and in other series of routine post-mortem examinations basophilic adenomas were found, frequently with no clinical findings referable to them.⁹⁻¹³

It may be concluded, then, that the prevailing opinion at present is that the likeliest finding in a patient exhibiting Cushing's syndrome is a tumor of the adrenal cortex. This is particularly true in cases in which sexual changes accompany the syndrome proper.

The importance to the surgeon of the relation between Cushing's syndrome and tumors of the adrenal cortex, apart from the necessity of investigating the adrenal glands in all cases of the syndrome, lies in the fact that the prognosis for recovery after operative removal of such a tumor associated with Cushing's syndrome is much poorer than when symptoms of virilism alone are present. Thus, Thompson and Eisenhardt¹² found that in 22 surgical cases of adrenal tumor with Cushing's syndrome, 18 patients died of shock resembling adrenal insufficiency in the immediate postoperative period, whereas in cases of true virilism operative recovery is the rule. Cahill¹²⁻⁵ also notes that shock from adrenal insufficiency does not occur after the removal of nonhormonal tumors of the gland or in the cases marked by sex-hormone changes only. Although recognizing that patients with Cushing's syndrome have recovered after surgical removal of an adrenal tumor, Cahill points out that unrecognized metastases are often present, and he suggests that this fact may influence the immediate recovery. Undoubtedly, the explanation of the uniform picture of postoperative acute adrenal insufficiency lies in the functional or actual atrophy of the gland on the opposite side.

DIAGNOSIS

The diagnosis of a hormone-producing tumor of the adrenal cortex is made on the clinical examination of the patient, pertinent laboratory data and roentgenographic findings. Often, however, the diagnosis can be confirmed only by surgical exploration or autopsy.

Clinical Data

As emphasized by Cahill, the appearance of sexual precocity before puberty, pseudohermaphroditism in girls, heterosexual changes in adults and the development of Cushing's syndrome in either male or female, child or adult, are indicative of pathologic adrenal physiology, and determined effort must be made to prove or exclude the existence of the tumor in such cases.

When the tumor is suspected, the most important physical finding is a palpable mass in the region of the adrenal glands.

Laboratory Data

The laboratory tests indicated in addition to the routine blood counts and urinalysis are the blood chemical determinations of the nonprotein nitrogen, cholesterol and chloride, the glucose-tolerance curve and the assay of the excess urinary excretion of the male and female sex hormones. The latter tests are becoming increasingly important.

Lukens¹⁴ states that thirty separate chemical substances with the sterol nucleus having hormonal effects have been isolated from the adrenal cortex. These include regulators of water and salt distribution and excretion, carbohydrate, fat and protein metabolism, growth factors and sex development. The masculinizing sex hormones have been identified as 17-ketosteroids. These may be estimated colorimetrically. The feminizing hormones are similar to the estrogens.⁴

By biologic assay, Frank¹⁵ found that 7 out of 8 patients with adrenal carcinoma had elevated urinary estrogen excretion with a negative pregnancy test, and he concluded that the elevated estrogen finding was of value in differentiating a malignant growth from an adenoma. Wilhelm and Gross¹⁶ reported a case of Cushing's syndrome due to a large adrenal adenoma in which the urinary androgens were markedly elevated, with a normal estrogen level. Reilly¹⁷ has also reported a case in a six-and-a-half-year-old boy with sexual precocity due to an adrenal adenoma in whom the androgen excretion was that of an adult male, whereas the estrogen excretion was not elevated. In 2 cases of carcinoma of the adrenal gland in women — one of whom exhibited virilism and the other a Cushing's syndrome — Oppenheimer and Silver¹⁸ found the urinary estrogens markedly elevated. The feminizing tumor in an adult male case of Simpson and Joll,⁷ which showed an increase of estrogen excretion, was mentioned above. Marked elevation of both androgen and estrogen urinary excretion has been reported by Gross¹⁹ in the case of a three-and-a-half-year-old girl who showed a masculine habitus, and enlarged clitoris and pubic hair due to an adrenal carcinoma. On the other hand, cases with hormonal changes have been described in which the excretion of the urinary sex hormone has been normal, as in the case reported by Cahill of a Cushing's syndrome due to an adrenal tumor with no sex changes except amenorrhea.

Since the clinical differentiation between tumor of the adrenal cortex and cortical hyperplasia is difficult, owing to the fact that both lesions may present the same symptom complex, Talbot, Butler and Berman²⁰ have developed a method to distinguish between the two by fractional analysis of the 17-ketosteroids.

In summary, it may be stated that the demonstration of an elevated urinary excretion of androgenic and estrogenic substances is of value in the

diagnosis of an adrenal tumor if positive but that a tumor may be present with a negative test. More research and wider usage of these tests are necessary to establish their final clinical value.

X-ray Data

An adrenal tumor often shows up as a soft-tissue shadow in the plain roentgenogram. Another frequent and valuable finding is downward displacement of the kidney in the pyelogram.

The x-ray diagnosis of adrenal tumors has been amplified by visualization of the adrenal glands by perirenal insufflation of air or oxygen. This procedure has been popularized in this country by Cahill,²⁻⁵ who has done several hundred injections without significant untoward reaction. In essence, the procedure consists in the injection of air into the perirenal tissues with subsequent exposure of films at intervals of from six to thirty-six hours to bring out the adrenal contour by contrast. Fish²¹ reported 2 fatal cases from air embolism in approximately two hundred injections, and he recommends oxygen as preferable to air. Cope and Schatzki²² advocate a modified technic in which 200 cc of air is injected into the triangular fat pad below the kidney and report no complications in one hundred and sixty-three injections. Roome²³ advocates perirenal insufflation as preferable to surgical exploration when a tumor is suspected. Hyman and Wilhelm²⁴ on the other hand, believe that the information gained from perirenal insufflation is of limited value and that the method should be used only as a last resort on account of its dangers.

The use of pneumoperitoneum in the following case was of definite value, although not diagnostic.

CASE REPORT

G. E. B. (60316), a 24-year-old married woman, was admitted to the Dependents' Ward, United States Naval Hospital, Corpus Christi, Texas, on March 29, 1945, complaining of a tumor in the abdomen of 2 months' duration. The patient stated that she had always been well until she injured her back in 1942, while riding a roller coaster. Following this injury she was in a body cast for 10 weeks. After the accident, she failed to regain strength and had frequent episodes of nausea and vomiting. One year before admission an increased growth of hair on the face had prompted her to shave her face on several occasions. She had also noted an excessive growth of hair on the arms and legs. There had been a complete amenorrhea for 2 years prior to admission. This had been attributed to hypothyroidism, for which she had received thyroid therapy without improvement. She had been married 1 year before admission, and the libido was stated to be normal. No pregnancy occurred despite the fact that contraceptives were not used. Excessive dryness of the skin, puffiness of the face and increased fat deposits about the shoulder girdle, with no change in the body weight, had been noted for several months.

Six months before admission, the patient had a sudden hemoptysis, which was found to be tuberculous in origin. She was treated with bed rest and artificial pneumothorax at a state tuberculosis sanatorium. While under treatment for pulmonary tuberculosis, she developed pain in the left upper quadrant of the abdomen and a palpable mass led to admission to this hospital. There were no symptoms referable to the urinary tract.

The past and family histories were irrelevant except as stated above.

Physical examination revealed a fairly well developed and well nourished woman with a general appearance suggestive of Cushing's syndrome. The height was 63 inches, and the weight was 106 pounds. The skin was abnormally dry, with mild acne on the face. There was a "buffalo type" of obesity involving the neck and shoulder girdle. The face was puffy, and there was an excessive amount of male type of hair on the cheeks, upper lip and chin. There was no adenopathy of the neck, and the thyroid gland was normal to palpation. The breasts were somewhat atrophic. The thorax was normal in contour. Examination of the chest showed the left lung to be clear, with physical signs of pneumothorax on the right. The heart was normal. The blood pressure varied between 140/120 and 128/116. There were striae over the lower abdomen. The pubic hair line was of masculine distribution,

sulfonephthalein test showed normal renal function in both kidneys.

X-ray examination of the chest revealed the heart and great vessels within normal limits. The left lung field was clear. There was a partial pneumothorax on the right side. In the apex of the collapsed lungs there was an area of increased density interpreted as an old tuberculous lesion. A plain film showed a large oval shadow measuring 14 by 11 cm. lying just to the left of the 12th dorsal and 1st, 2nd and 3rd lumbar vertebrae, overlapping the lower two thirds of the kidney shadow. There was a 2-cm linear calcified shadow along its outer margin. Retrograde pyelograms revealed a normal kidney and ureter on the right. On the left, in addition to the mass, there was a slight hydronephrosis and hydroureter, apparently unrelated to the mass (Fig 1).



FIGURE 1 Retrograde Pyelogram Showing Mass on the Left Side

extending toward the umbilicus. There was a palpable, tender, round tumor in the left upper quadrant, extending into the left flank. It was movable and descended with inspiration. There was no fixation to the abdominal wall. The tumor measured approximately 10 by 15 cm.

The external genitalia were normal, with no hypertrophy of the clitoris. Pelvic examination revealed an infantile uterus with no masses in the adnexal regions. The extremities appeared slender in proportion to the trunk. There was an excessive growth of fine hair on the arms and legs.

Examination of the blood disclosed a red-cell count of 5,100,000, with a hemoglobin of 15 gm, and a white-cell count of 10,000, with a normal differential. The fasting blood sugar was 80 mg, the blood cholesterol 140 mg, and the nonprotein nitrogen 28 mg per 100 cc. The blood Kahn reaction was negative. The urine was normal. The sedimentation rate was 21 mm in 1 hour.

Cystoscopic examination showed a normal bladder, with no obstruction to passage of ureteral catheters on either side, specimens obtained from each kidney were normal on microscopic examination and were sterile on culture. A phenol-

There was no evidence of distortion or displacement of the kidney by the tumor. Stereoscopic views localized the tumor anterior to the kidney and posterior to the transverse colon. A pneumoperitoneum was performed, and films in several planes confirmed the location of the tumor as shown in previous films.

The preoperative diagnosis was Cushing's syndrome due to adrenal tumor. The pulmonary tuberculosis was considered to be coincidental and, since the process was controlled, not to contraindicate surgery.

On April 13 the patient was operated on under spinal anesthesia. A transverse incision was made from the outer border of the left rectus muscle extending laterally approximately 15 cm. The incision was deepened to the perirenal space, and the kidney was explored and found to be normal. Further exploration of the wound anteriorly and extraperitoneally revealed a soft, encapsulated, ovoid tumor, the size of a grapefruit, with a vascular pedicle on its upper medial aspect.

The tumor was mobilized from a few light surrounding adhesions, and the pedicle was clamped, cut and ligated. A

search for the left adrenal gland failed to disclose any semblance of adrenal tissue. The wound was closed in layers with a cigarette drain.

The pathological report, by Dr H B Willford was as follows:

Grossly the specimen consists of a large, oval encapsulated, soft tumor measuring 13 by 9 cm. On section the tumor tissue is golden yellow, edematous and supported by a fibrous reticulum (Fig 2).

On microscopic examination the tumor cells are arranged in small groups separated by fine connective-tissue strands (Fig 3). No lumens are present. The cell nuclei are hyperchromatic to pale and vary in size. Most of the

of plasma, glucose and saline and intramuscular injections of desoxycorticosterone. The patient showed a transitory response and regained consciousness temporarily after each injection of the hormone. Despite the supportive treatment, however, she gradually became weaker and expired 48 hours after operation.

Autopsy At post-mortem examination, which excluded the head and was done 2 hours after death, the external appearance was the same as that on physical examination. There were nodules of active tuberculosis in the apex of both lungs, the right lung was partially collapsed. The operative incision was clean, as was the site from which the tumor had been removed. All ligatures were intact, and there was no evidence of hemorrhage. No sign of adrenal tissue remained

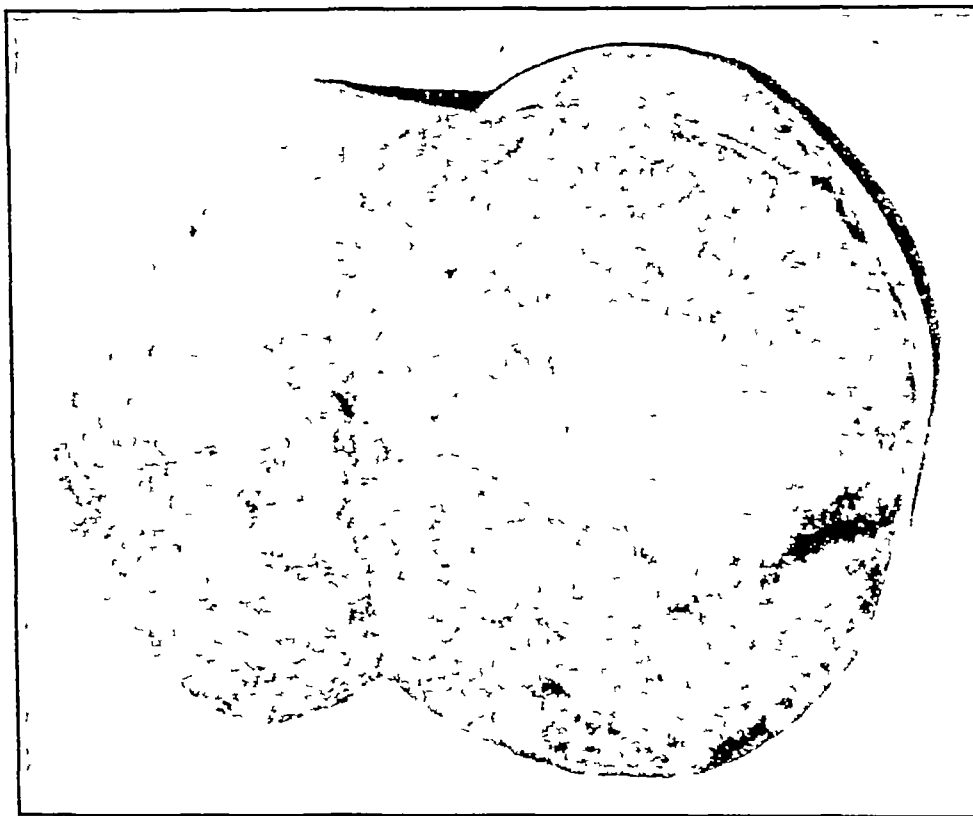


FIGURE 2 Photograph of the Tumor after Removal

tumor cells show a cytoplasm of granular, foamy texture and stain a faint pink. Vascularity is generally good but becomes sparse centrally. There is no true degeneration. Along many of the blood-vessel spaces, large granular and fatty-appearing cells are present. A few giant cells are noted, with large granular nuclei or multiple nuclei. This is considered to be an adrenal tumor of the zona glomerulosa type.

Diagnosis Malignant adenoma of the adrenal cortex.

The postoperative course for the first 24 hours was uneventful. There was no evidence of shock. The temperature was 99.8°F, the pulse 105, and the respirations 20. The blood pressure was 132/98. At the end of 36 hours, however, the patient's condition began to change for the worse. The pulse rose to 160, and the temperature began to climb rapidly, reaching 106°F before death. The respirations rose to 30 and became shallow. The patient's color was ashen. The blood pressure became imperceptible, and she relapsed into a semicomatose state. Supportive treatment, which was started immediately after the patient began to show signs of collapse, included 100 per cent oxygen in a tent, transfusions

on the left. The uterus and ovaries were infantile in character, with no corpora lutea. The most striking finding was the complete absence of the right adrenal gland. Prolonged systematic search of the retroperitoneal tissues and the abdominal contents showed no vestige of adrenal tissue, and no adrenal blood supply could be identified. There was no evidence of tuberculous involvement of these tissues. It was the opinion of the pathologist, as well as of all present at the autopsy, that this case represented a congenital aplasia of the right adrenal gland and that at the time of death there was no adrenal tissue in the body.

The wisdom of demonstrating an adequate adrenal gland on the side opposite the tumor is apparent from this case. It was so obvious, however, that the patient's well-being and life were jeopardized by the tumor that its immediate removal seemed justified, and the ultimate outcome would have been the same had surgery been withheld.

STATE OF THE ADRENAL GLAND OPPOSITE TO THAT CONTAINING TUMOR

Although it had previously been noted that in tumor of the adrenal cortex the contralateral gland exhibited varying degrees of atrophy, Cecil,²⁵ in 1933, was the first to emphasize this fact when he reviewed the literature and found that in 30 per cent of cases the adrenal gland on the side opposite the tumor was either absent or atrophic to an extent insufficient to support life. Cecil considered the process in cases of reported absence of the gland to be one of advanced atrophy rather than true aplasia.

In 1941 Weinberg,²⁶ in a review of 34 cases of neoplasm of the adrenal cortex occurring in the preceding fourteen years in which the clinical ob-

amples of this process in other endocrine glands are found in the involution of the insulin-forming beta cells of the pancreas that accompanies tumors of the islands of Langerhans, and the atrophy of the normal parathyroid glands that takes place in the presence of a parathyroid tumor. Furthermore, excess administration of estrogenic substances has been noted to cause involution of the ovaries, and similar changes in the testicles have been induced by excess androgenic hormone injection. Selve²⁷ has proposed the term "compensatory atrophy" for this phenomenon.

From the experimental point of view, Ingle and Kendall²⁸ started with the observation that transplants of the adrenal glands do not regenerate in the presence of one intact gland and demonstrated that the administration of large amounts of corti-

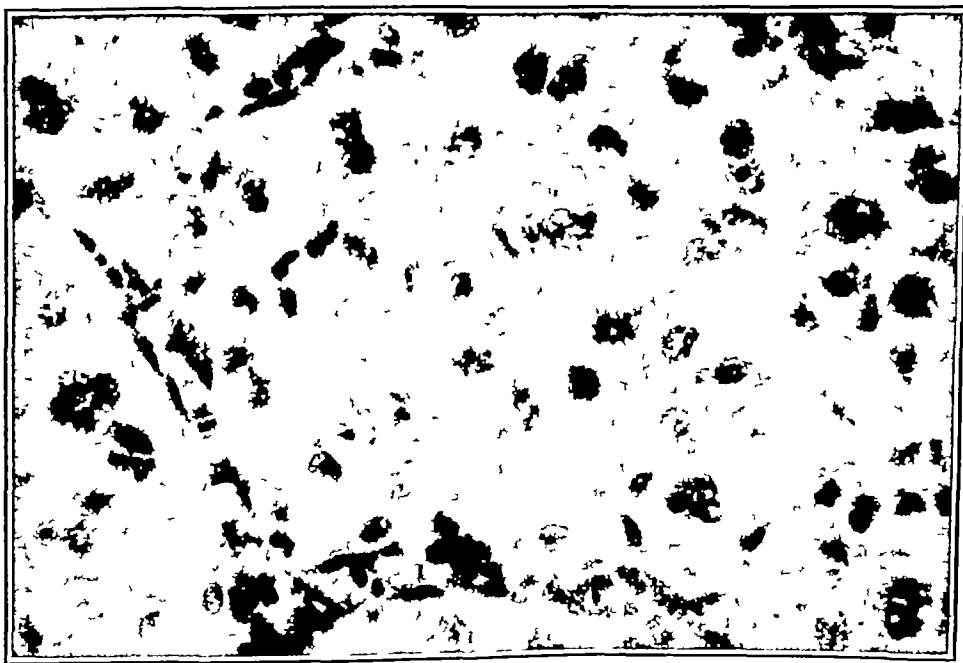


FIGURE 3 Photomicrograph of a Section of the Tumor

servations on the state of both adrenal glands had been confirmed at autopsy, found that atrophy was encountered in 21 cases, or 62 per cent, and that the gland was completely absent in 2 cases. In 10 cases the gland was reported as "grossly normal." He also described a case in which bilateral adrenal atrophy had been caused by a tumor of an accessory adrenal gland.

The cause of this glandular atrophy on the supposedly normal side is excess production of the metabolic hormones by the tumor, with consequent suppression of function of the normal tissue. From the teleologic standpoint, the tumor relieves the normal gland of the necessity of functioning. Ex-

to normal rats produced atrophy of the adrenal cortex. They found this effect to be mediated through the adrenotropic principle of the anterior portion of the pituitary gland.

In 1926 Feinblatt²⁹ reported the case of a thirty-two-year-old woman with virilism dying of exhaustion, who at autopsy showed a carcinoma of the right adrenal gland and a complete absence of the one on the left. In 1927 Gordon and Browder³⁰ described a case of a left suprarenal carcinoma causing puberty praecox in a three-year-old boy who died of pulmonary metastases, and at autopsy no suprarenal gland was found on the right. Lukens et al,³¹ in 1937, reported the case of a twenty-nine-

year-old woman with Cushing's syndrome who was operated on with removal of an encapsulated tumor from the right adrenal gland and died on the eighth postoperative day of shock. Autopsy revealed complete absence of the left adrenal gland and the residual adrenal tissue on the right side to be about half the normal size. Lukens stated that the autopsy files of the University of Pennsylvania Hospital from 1894 to the date of his report contained records of 3 additional cases of absence of the gland, none, however, had been associated with contralateral tumor. Absence of the left adrenal gland was found on surgical exploration by Goldheizer²² in the case of an eighteen-year-old girl with hirsutism, the right adrenal gland in this case was enlarged but no extirpation of tissue was done in view of the missing left gland.

Cahill,² using perirenal insufflation in investigating several hundred cases of suspected adrenal disease, found that in 9 per cent only one adrenal gland could be demonstrated by this method.

TREATMENT

The treatment of these tumors is primarily by surgical removal. The operation is doomed to failure, however, unless a carefully planned program to counteract postoperative acute adrenal insufficiency due to reduced function of the opposite gland is carried out. According to Cahill the most important factor in the surgical management of these cases is the anticipation, prevention or control of such failure.

At the time of the operation it is essential to determine both the presence of the supposedly normal gland and its capacity to support life. In some cases in which the opposite gland was described as half the normal size, the patients have recovered.²³

From the technical standpoint, two surgical approaches are frequently used — namely, the lumbar extraperitoneal route and the abdominal transperitoneal route. Transthoracic access to the adrenal glands has been described but has found little popularity in the literature. Walters²⁴ recommends exposure of both glands and uses the usual loin-kidney incision. Young²⁴ explores both glands simultaneously through the lumbar regions, using a specially devised spreader type of retractor. Cahill² recommends the anterior, abdominal, transperitoneal approach through an oblique subcostal incision as giving the best exposure and permitting exploration of the opposite gland through the same incision.

All who have had experience with the surgical removal of tumors of the adrenal cortex emphasize that immediate aggressive postoperative steps must be taken to combat acute adrenal insufficiency. The majority of deaths occur in from twenty-four to forty-eight hours after operation of collapse, which does not respond to the usual antishock therapy of fluids, blood transfusion and stimulants. If ade-

quate amounts of adrenocortical extract are given, however, it may be expected that the remaining adrenal tissue will regain its capacity to produce a sufficient amount of the hormones essential to life. Walters, who has successfully operated on 10 patients, attributes his success to the availability of potent adrenocortical preparations to tide the patient over the critical period immediately after operation.

In a case of Cushing's syndrome due to an adenoma in which the patient was successfully operated on, Wilhelm and Gross¹⁶ used the blood-pressure readings as a guide for the dosage of adrenocortical extract. They point out that there is a danger of overdosage as shown by the development of oliguria and anasarca from the seventh to the twelfth postoperative day. Grollman²⁵ suggested a dosage of 200 rat units of adrenocortical extract a day as appropriate for the immediate postoperative period.

PROGNOSIS

It should be recalled that postoperative fatalities are much more frequent in the cases with metabolic changes than in those in which sexual changes predominate.

In 1933 Cecil²³ stated that in 39 per cent of the operated cases the patients died of shock caused by adrenal deficiency. In 1941 Weinberg²⁶ wrote that the outcome is usually fatal shortly after surgery. In 1943 Thompson and Eisenhardt¹² found that in 22 cases of adrenal tumor with Cushing's syndrome, 18 patients who were operated on with removal of the tumor died in the immediate postoperative period of shock resembling adrenal insufficiency. In a few cases death occurred in spite of "fairly adequate" measures to combat the deficiency.

SUMMARY

The subject of hormone-producing tumors of the adrenal glands is reviewed, with reference to classification, relation to Cushing's syndrome, diagnosis, treatment and prognosis.

A case of Cushing's syndrome due to an adrenal tumor is reported in which the patient died of acute adrenal insufficiency thirty-six hours after operative removal of the tumor and in which, at autopsy, complete absence of the opposite adrenal gland was found. This is the fourth such case in the literature.

From a review of the available literature it is concluded that an increasing number of successful operative removals are being done owing to better postoperative therapy. The prognosis, however, is still exceedingly grave in the cases associated with Cushing's syndrome, because of the atrophy and insufficiency of the supposedly normal gland.

REFERENCES

1. Grollman A. K. *The Adrenals* 410 pp. Baltimore: Williams and Wilkins Company 1936.
2. Cahill G. F. Tumors of adrenal and use of air insufflation in their diagnosis. *Radiology* 37: 533-544, 1941.

- 3 Cahill, G F, Melicow, M M, and Darby, H H Adrenal cortical tumors: types of nonhormonal and hormonal tumors *Surg Gynec & Obst* 74 281-305, 1942
- 4 Cahill, G F Hormonal tumors of adrenal gland *Pennsylvania M J* 47 655-667, 1944
- 5 *Idem* Hormonal tumors of adrenal *Surgery* 16 233 265, 1944
- 6 Collett, A Genito-suprarenal syndrome (suprarenal virilism) in girl one and a half years old, with successful operation *Am J Dis Child* 27 204-218 1934
- 7 Simpson, S L, and Joll, C A Feminization in male adult with carcinoma of adrenal cortex *Endocrinology* 22 595-601 1938
- 8 Cushing H Basophil adenomas of pituitary body and their clinical manifestations (pituitary basophilism) *Bull Johns Hopkins Hosp* 80 137-195, 1932
- 9 Susman, W Adenoma of pituitary, with special reference to pituitary basophilism of Cushing *Brit J Surg* 22 539 544 1935
- 10 Dorfman R I, Wilson H M, and Peters, J P Differential diagnosis of basophilism and allied conditions *Endocrinology* 27 1-15, 1940
- 11 Farber, J E, Gasteria, F J, and Postoloff, A V Cushing's syndrome in children: review of literature and report of case *Am J Dis Child* 65 593 603, 1943
- 12 Thompson, K W, and Eisenhardt L Further consideration of Cushing syndrome *J Clin Endocrinol* 3 445-452 1943
- 13 Anderson, E, and Haymaker W Cushing's syndrome *J Nerv & Ment Dis* 99 511-520 1944
- 14 Lukens F D W Diagnosis and treatment of disorders of adrenal glands *M Clin North America* 26 1803 1815 1942
- 15 Frank R T Estrogenic reaction in adrenal cortical carcinoma *J Mt Sinai Hosp* 8 514-519, 1942
- 16 Wilhelm S F and Gross S W Surgical removal of adrenal adenoma with relief of Cushing's syndrome *Am J M Sc* 207 196-204 1944
- 17 Reilly W A Adrenal cortical tumor causing sexual precocity in child: successful treatment of coma shock and hemorrhage preceding operation *Clinics* 1 669 676 1942
- 18 Oppenheimer, B S and Silver, S Variability in pathological findings in Cushing's syndrome: report of six cases *Tr A Am Physicians* 52 146-163 1937
- 19 Gross, R E Neoplasms producing endocrine disturbances in childhood *Am J Dis Child* 59 579 628, 1940
- 20 Talbot, N B, Butler, A M, and Berman R A Adrenal cortical hyperplasia with virilism: diagnosis, course and treatment. *J Clin Investigation* 21 559 570 1942
- 21 Fish G W Discussion of Roome's
- 22 Cope O, and Schatzki R Tumors of adrenal glands I Model: air injection roentgen technic for demonstrating cortical and medullary tumors *Arch Int Med* 64 1222 1238 1939
- 23 Roome N W Visualization of adrenal glands by air injector *J A M A* 112 196-198, 1939
- 24 Hyman A and Wilhelm S F Differential diagnosis of renal and suprarenal tumors *J Urol* 40 737-751, 1938
- 25 Cecil, H L Hypertension obesity virilism and pseudohypertension as caused by suprarenal tumors *J A M A* 100 463-469 1933
- 26 Weinberg T Contralateral adrenal atrophy associated with contralateral adrenal neoplasms *New York State J Med* 41 384-394 1941
- 27 Selye H Compensatory atrophy of adrenals *J A M A* 115 2246-2252, 1940
- 28 Ingle, D J, and Kendall E C Atrophy of adrenal cortex of rat produced by administration of large amounts of cortin *Science* 64 245, 1937
- 29 Feinblatt H M Carcinoma of cortex of suprarenal gland with virilism: report of case with necropsy *Arch Int Med* 38 462-473 1926
- 30 Gordon M B and Browder E J Suprarenal carcinoma with pubertas praecox in boy three years of age *Endocrinology* 11 265 278 1927
- 31 Lukens F D W Flippin H F and Thigpen, F M Adrenal cortical adenoma with absence of opposite adrenal: report of case with operation and autopsy *Am J M Sc* 193 812 820 1937
- 32 Goldheizer M A *The Adrenal Glands in Health and Disease* 77 pp Philadelphia T A Davis Company 1945 P 525
- 33 Waiters W Surgical lesions of adrenal glands *South M J* 34 1241-1247, 1941
- 34 Young H H *Genital Abnormalities Hermaphroditism and Related Adrenal Diseases* 649 pp Baltimore Williams and Wilkins Company, 1937
- 35 Grollman A Personal communication

ACUTE APPENDICITIS OCCURRING DURING THE COURSE OF OTHER DISEASES*

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THE diagnosis of acute appendicitis is usually considered whenever a patient develops symptoms or signs suggesting an acute intra-abdominal inflammatory lesion. There are many contributions dealing with the differential diagnosis of abdominal symptomatology, in which many diseases that mimic appendicitis are enumerated and classified. The inference usually drawn is that laparotomy on the basis of an erroneous diagnosis of acute appendicitis is warranted if some morbid process is encountered to account for the clinical picture, such as a twisted ovarian cyst, inflamed Meckel's diverticulum, regional ileitis, neoplasm, volvulus or intussusception. Emphasis is usually placed, however, on the dangers of operating on a patient whose abdominal complaints are based on some other underlying systemic or regional disorder. Prominent among the more frequent of these diseases are pneumonia, tonsillitis, upper respiratory infections, pyelitis, cardiac failure, mesenteric thrombosis, diabetic ketosis and syphilis of the central nervous system. It is beyond the scope of this communication to undertake a discussion of these diseases and the features in the differential diagnosis that distinguish them from appendicitis. The problems of diagnosis and operative indications are particularly compli-

cated in patients already hospitalized, or under treatment for some nonrelated disorder, who, under observation, develop acute abdominal complaints referable to the lower abdomen. Although under ordinary circumstances such symptoms are sufficiently specific to warrant a diagnosis of appendicitis, under these special conditions there is a tendency to dismiss the possibility of an independent lesion, and to attempt to correlate the new symptomatology with the pre-existent disorder. The delay in therapy thus engendered may be prejudicial to the interests of the patient, whose best chance for recovery may depend on removal of the acutely inflamed appendix.

It is the purpose of this paper to emphasize the necessity for laparotomy in the presence of persisting symptoms and signs ordinarily associated with acute appendicitis, despite the pre-existence or coexistence of other diseases that include abdominal complaints among their possible manifestations. The following cases are illustrative.

CASE 1 J T (MSH 503817), an 8-year-old girl, previously in good health, was admitted to the hospital on April 6, 1943, suffering from an acute respiratory infection of 24 and abdominal pain of 6 hours' duration. On the previous day, she had begun to cough, and a sore throat and coryza had been noted. Six hours before admission she had begun to experience abdominal pain localized to the region of the umbilicus and had vomited three times. On examination, the temperature was 98.8°F, the pulse 78, and the respirations 24. A purulent pharyngitis was present.

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together with greatly enlarged, reddened tonsils. There was a generalized lymphadenopathy, and the spleen was palpated one fingerbreadth below the left costal margin. The abdomen was soft, with persistent tenderness in the right lower quadrant. Rectal examination disclosed no tenderness. Examination of the blood revealed a white-cell count of 18,100, with 73 per cent neutrophils and 22 per cent lymphocytes. An appendectomy performed shortly after admission disclosed an acute phlegmonous appendicitis. The convalescence was uneventful. A throat culture revealed beta-hemolytic streptococcus and alpha-hemolytic streptococci. Blood for heterophil agglutination was positive in a dilution of 1:16.

CASE 2 A C (M S H 486225), a 14-year-old boy, was admitted to the hospital on February 27, 1942, with a history of abdominal pain, which had shifted to the right lower quadrant, and vomiting of 2 days' duration. The onset of pain was associated with a sore throat and a temperature of 101°F. On examination, the temperature was 101°F, the pulse 80 and the respirations 20. The patient appeared acutely ill, and complained of severe pain in the lower abdomen. There was a marked postnasal discharge, and white follicles were present on the right tonsil. The peripheral lymph nodes were slightly enlarged. Lower abdominal tenderness was present chiefly in the right lower quadrant, with some rigidity to the right of the umbilicus. Rectal examination revealed tenderness on the right side. Urinalysis showed a slight trace of albumin. Shortly after admission, an appendectomy was performed, the appendix revealing acute inflammation. The nasopharyngitis subsided, and the patient was discharged on the 8th postoperative day.

CASE 3 O G (M S H 454412), a 32-year-old painter, was admitted to the hospital on March 29, 1940, with complaints of a severe sore throat, general malaise and fever of 3 days' duration. During 12 hours prior to admission he had experienced pain in the right lower quadrant with radiation to the epigastrium, followed by vomiting. The pain in the lower abdomen became progressively severer. On examination, the temperature was 100°F, the pulse 92, and the respirations 26. The patient appeared acutely ill. Marked follicular tonsillitis was present. There were both tenderness and spasm in the right lower quadrant. Appendectomy was performed promptly, and an acute gangrenous appendicitis was encountered. Postoperatively the temperature rose to 104°F, associated with an increase in the follicular tonsillitis. Sulfanilamide was given, and the temperature subsided to normal on the 4th day, with corresponding clinical improvement. The wound healed by primary union, and the patient was discharged on the 8th postoperative day.

CASE 4 H B (M S H 488688), a stocky 50-year-old man, was admitted to the hospital on April 21, 1942, complaining of lower abdominal pain of 48 hours' duration. The diagnosis of diabetes mellitus had been established 15 years previously, and the disease had been controlled during this period by dietary regulation without insulin. On examination, the temperature was 100.2°F, the pulse 90, and the respirations 26. Moderately advanced neuroretinopathy was present. There was localized tenderness, without spasticity, in the right lateral portion of the abdomen near the level of the umbilicus, no tenderness could be elicited on rectal examination. Urinalysis revealed a +++ test for sugar but no acetone. During a 24-hour period, the diabetes was brought under control with insulin, there was no increase in symptomatology, and no further temperature elevation. Lower abdominal pain and tenderness persisted, and operation disclosed the appendix as the seat of an acute phlegmonous inflammation. The postoperative course was uneventful, the wound healing by primary union, and the patient was discharged on the 12th day, when he was receiving 20 units of protamine insulin daily and was sugar free on a daily diet of 150 gm of carbohydrate, 80 gm of protein and 80 gm of fat.

CASE 5 L S (M S H 497398), a moderately obese, 45-year-old man, entered the hospital in November, 1942, with an acute myocardial infarction, pericarditis and cardiac decompensation. A subtotal gastrectomy for duodenal ulcer had been performed in July, 1938, after 9 years of unsuccessful medical treatment. On admission, the temperature was 102°F, the pulse 100, and the respirations 30. A pericardial friction rub was present, and the heart sounds were of only fair quality, coarse rales were heard at both lung bases. The

electrocardiographic changes were those of an acute infarction of the posterior wall. On the 3rd hospital day the patient developed a left hemiparesis, which was attributed to a cerebral embolus from a detached mural thrombus. The temperature gradually subsided, the sedimentation time rose to normal, the friction rub became intermittent, and the signs of both the hemiparesis and the congestive failure began to clear. Thirty-seven days after admission, lower abdominal cramps, followed by nausea and vomiting, developed. There was tenderness without spasm in the right lower quadrant and some tenderness to the right on rectal examination. The temperature remained normal. Examination of the blood showed a white-cell count of 15,300, with 78 per cent neutrophils — 2 weeks previously the white-cell count had been 11,200, with 66 per cent neutrophils. Examination of the stool for occult blood was negative.

Because of the bizarre clinical course, with recurrent pericarditis, pneumonia, hemiparesis and microscopic hematuria, the possibility of a vascular basis for the abdominal symptomatology was considered. Among the diagnoses entertained were mesenteric thrombosis and periarteritis nodosa. The patient was observed for about 8 hours, during which the symptoms and signs persisted without much change. After a surgical consultation laparotomy was performed disclosing acute phlegmonous appendicitis. The postoperative course was uneventful.

CASE 6 F P (M S H 503543), a 32-year-old man, was admitted to the hospital on March 26, 1943. He had been awakened 8 hours previously by pain in the right lower quadrant that was nonradiating and was associated with nausea, without vomiting. Three years previously he had contracted syphilis and gonorrhea, both of which had been treated intensively, antisyphilitic therapy was still being administered. On examination, the temperature was 100°F, the pulse 108, and the respirations 32. There was tenderness in the right lower quadrant, with slight spasm. Rectal examination disclosed tenderness to the right. Despite the clear-cut evidence of acute appendicitis, there was a tendency on the part of some observers to interpret the clinical picture in terms of syphilitic changes. Appendectomy was promptly performed, however, and disclosed an acute phlegmonous appendicitis.

CASE 7 R L (M S H 452212), a 13-year-old girl, with an indefinite 4-year history of "kidney trouble," was admitted to the hospital on February 7, 1940. On the morning of admission she complained of abdominal distress, followed by severe epigastric cramps, vomiting and radiation of the pain to the right lower quadrant. A similar episode had occurred 1 year previously. On examination the patient did not appear acutely ill. The temperature was 102°F, the pulse 140, and the respirations 28. The abdomen was soft, with slight generalized tenderness referred to the right lower quadrant and maximum direct tenderness just below McBurney's point. There was slight rectal tenderness on the right. The white-cell count was 12,800 with 92 per cent neutrophils. Urinalysis showed a +++ test for albumin, with many coarse cellular casts and rare red cells per high-power field. The blood urea nitrogen was 9 mg per 100 cc, the blood Wassermann reaction was negative. In spite of the chronic glomerulonephritis and the atypical clinical picture, appendectomy was performed on the 2nd hospital day because of the persistence of spontaneous pain and tenderness. Acute appendicitis and lymphoid hyperplasia were found. The postoperative course was smooth, but characterized by persistent albuminuria and a blood pressure ranging about 150/80.

CASE 8* H C (M S H 450278), an 18-year-old Negro, was admitted to the hospital on December 23, 1939. For 2 years there had been an intermittent purulent discharge from the right ear. Stiffness of the right side of the face and drooping of the right side of the mouth had been increasingly more troublesome for the preceding 4 days. Several months previously the patient had worked for a short time at the Bronx Zoo. The temperature, pulse and respirations were normal.

Physical examination disclosed a well developed and well nourished man lying quietly in bed with eyes closed, head drawn back, legs extended and arms flexed. There was a coarse horizontal nystagmus on left lateral gaze, the eye

*This case was reported with special reference to the otologic features by Rosen.¹

grounds were not remarkable. A posterior marginal perforation of the right ear drum was present, with a small amount of thin, pulsating, nonfoul discharge, there was no tenderness over the mastoid process. The left ear drum was normal. Slight trismus was noted. Boardlike rigidity of the abdominal musculature was present, without tenderness. There was considerable increase in tone in the arms, and passive movement of the legs was difficult because of rigidity. The neck could not be flexed, but could be moved from side to side. The tendon reflexes in the arms were depressed, and those in the legs were decreased and jerky. No pathologic reflexes could be elicited. The patient was rational and talked slowly and carefully.

Shortly after admission the patient experienced a generalized, true tetanic convulsion, characterized by marked opisthotonos, without clouding of consciousness. Several such episodes occurred within a short period, each precipitated by noise or trauma, such as movement. A lumbar tap revealed clear spinal fluid under normal pressure, with normal dynamics, there were no significant cellular or chemical changes. The convulsive state soon became quite difficult to control, and almost constant opisthotonos was present. Extremely deep anesthesia was needed to obtain relaxation, and within a 5-hour period the patient received 70 mg. of Avertin per kilogram of body weight by rectum and 0.5 gm. of sodium amytal, and 100 mg. of Avertin per kilogram of body weight intravenously as well as deep ether anesthesia. Despite all sedation the rigidity persisted, and it was necessary to repeat the ether frequently. On the night after the practically permanent convulsive state, marked stridor developed, and artificial respiration was required several times. Because of extreme swelling of the tongue and episodes of laryngeal spasm, a tracheotomy was performed.

Large doses of tetanus antitoxin were administered intravenously—100,000 units a day for 2 days, followed by 50,000 units every other day, with a progressive reduction to 5000 units every 3 days. On the day after the onset of the convulsions the temperature rose to 104°F, the pulse to 140, and the respirations to 50 to 60, and the patient became incontinent. A bilateral bronchopneumonia, involving large portions of both lower lobes, was treated by 0.6 per cent sulfapyridine intravenously. The white-cell count rose from normal to 15,000, but a blood culture was negative. At the end of 5 days the patient's condition was still poor, with a temperature of 105°F and gasping respirations. Although the tetanic state was gradually being controlled, the treatment of the pneumonia was the chief problem, and the patient required an oxygen tent and constant special nursing care. At that time smears taken from the right ear were reported as showing a variety of organisms, including proteus and tetanus bacilli and the enterococcus. The pathogenicity of the tetanus bacilli was established by demonstration of their toxin-producing properties on bacteriologic investigation. There was a gradual recession of the rigidity, and the pneumonia slowly cleared. The temperature returned to normal, the tachycardia persisted, and there were occasional mild serum reactions.

A month after admission, while approaching convalescence, the patient developed abdominal cramps, without vomiting. The abdominal wall presented the extreme rigidity characteristic of tetanus, and there was localized tenderness over McBurney's point. In addition, there was evidence of mild serum sickness, with generalized lymphadenopathy and eosinophilia. Over a period of 12 hours' observation, the symptoms and signs persisted unchanged. The temperature remained normal. Examination of the blood showed a white-cell count of 14,900, with 68 per cent segmented, and 14 per cent nonsegmented neutrophils, 15 per cent eosinophils and 3 per cent monocytes, 8 days previously the count had been 11,300, with 44 per cent segmented and 8 per cent nonsegmented neutrophils, 31 per cent lymphocytes, 12 per cent monocytes and 5 per cent eosinophils. Despite the obvious reasons for possible temporizing in this case, operation appeared imperative once the diagnosis of acute appendicitis had been made. The patient was given 120 mg. of procaine as a spinal anesthetic, with no demonstrable relaxation of the abdominal musculature. The pathological report was "acute phlegmonous appendicitis."

Following recovery the patient underwent a modified right radical mastoidectomy, in an attempt to eliminate the primary focus of the tetanus. He was discharged from the hospital on March 4, and the tracheotomy was allowed to close.

Follow-up observation for 2 years showed him to be in good general health.

CASE 9 F L (M S H 501896), a 22-year-old man in good health, was admitted to the hospital on February 19, 1943, for the repair of a small, asymptomatic, right, indirect, inguinal hernia that had been detected in the course of a physical examination for induction into the Navy. There were no other physical defects. Urinalysis was negative, the white-cell count was 8300. On February 20, a right hernioplasty was performed under local (novocain) anesthesia. During the 1st week the postoperative course was uneventful, and the temperature at no time rose above 99°F. The patient was awakened at 4 o'clock on the morning of the 8th postoperative day with pain below the umbilicus, followed by nausea and unsuccessful attempts to vomit. The temperature was 97°F, and the pulse rate 60. The pain subsided in a short while, after the passage of flatus. Abdominal examination disclosed slight tenderness in the right lower quadrant, without spasm. There was no evidence of a wound infection. Under observation, slight pain recurred in the right lower quadrant, and the tenderness became more marked. The temperature rose to 99°F, the white-cell count to 12,800, with 90 per cent segmented and 3 per cent nonsegmented neutrophils. An appendectomy was performed 15 hours after the onset of symptoms. Pathological examination disclosed an acute phlegmonous appendicitis. Convalescence thereafter was without incident.

CASE 10 E Y (M S H 502446), a 10-year-old girl, was admitted to the hospital in March, 1943. Three years previously, following aspiration of an Indian nut, she had been treated at another hospital for "pneumonia," and a thoracotomy had been performed for empyema. The evidence of pulmonary suppuration had persisted. Shortly after admission a lobectomy of the left upper lobe, performed for numerous nonputrid pulmonary abscesses, was followed in 10 days by a drainage operation for empyema. On the 14th postoperative day the patient became nauseated and vomited several times, but there was no abdominal pain or tenderness. On the following day she was still nauseated, but did not vomit. She complained of periumbilical pain, and there was direct tenderness in the right lower quadrant. The pulmonary status contraindicated any surgery unless it was imperative.

An appendectomy revealed acute appendicitis. The patient withstood the operation well. Two weeks later a left hemiparesis developed, and death occurred on the day after operation for a large metastatic brain abscess secondary to intrathoracic suppuration.

These cases are not unique. They were selected, not from a review of the hospital records but from the large number of cases of acute appendicitis seen on an active surgical service over a three-year period. In common, they all represented appendicitis occurring in the course of other diseases.

The first 3 cases illustrate one of the most frequent problems concerned with abdominal symptomatology. Leaving aside the moot question of the relation between tonsillar (and upper respiratory) infection and acute appendicitis, the widespread distribution of upper respiratory infections during the winter months makes its coincidence with acute appendicitis inevitable in some patients. Although an unnecessary laparotomy performed on a patient with tonsillitis or an upper respiratory infection may contribute to the development of a more serious pulmonary complication, the consequences of neglecting an acutely inflamed appendix may be even more profound. Fever may be due to obvious nasopharyngitis or to a suspected appendicitis. The presence of a leukocytosis, as demonstrated either by the total white-cell count or by the differ-

ential count, is of no differential aid. Attention is called to the study of Medlar,² who in 1929 analyzed the variations in the white-cell counts of normal persons. In the series of 506 children with acute appendicitis reported by Scott and Ware,³ the white-cell count was below 10,000 in 17 children who presented perforation with peritonitis or abscess. In 1 case (M S H 497693), the white-cell count fell from 11,000 to 7500 in a patient with pain in the right lower quadrant and microscopic hematuria who was suspected of harboring a ureteral calculus, the disease was revealed at operation to be acute phlegmonous appendicitis. The current attitude of most surgeons on the subject of the white-cell count in the diagnosis of acute appendicitis may be summed up in Johnson's⁴ plea not to trust blindly to a low white-cell count as conclusive evidence against appendicitis, or to a high one as overwhelming evidence in favor of operation and by a similar statement in a review of cases of appendicitis in pregnancy by Twyman, Mussey and Stalker.⁵ In the presence of an acute upper respiratory infection the diagnosis of appendicitis must rest on clinical grounds.

The evaluation of abdominal pain in a person suffering from diabetes, cardiac disease, syphilis or nephritis involves many considerations. The point to be made is that these patients possess the same potentialities for developing acute appendicitis as other persons, episodes of abdominal symptoms and signs ordinarily suggestive of acute appendicitis should continue to be so regarded. Indeed, it can be contended with considerable justification that a patient suffering from a serious systemic disease has a far greater chance for survival if operated on in the uncomplicated than in the later stages of acute appendicitis. A similar situation exists in abdominal pain in the course of the contagious diseases of childhood. In the series reported by Goodman and Silverman,⁶ in more than half the cases of acute appendicitis, the appendix was found to have perforated at the time of operation. Delayed operation was at least in part attributable to an attempt to interpret the abdominal pain as a possible manifestation of the infectious disease. The difficulty of establishing an early diagnosis in young children is further attested by Scott and Ware,³ who point out that in children under six years of age perforation was encountered more than twice as often as simple acute appendicitis without rupture.

In the case of tetanus (Case 8) presented above, many unusual medical and otologic features were evident and the abdominal rigidity rendered the diagnosis of an acute intraperitoneal inflammatory process difficult. In the patient convalescing from

a right-sided hernioplasty performed a week previously (Case 9), careful consideration had to be paid both to the site and to the circumstances of the first operation. Case 10 illustrates the occurrence of acute appendicitis in the course of unrelated pulmonary suppuration.

Acute appendicitis has been recorded in the course of acute anterior poliomyelitis,⁷ Addison's disease⁸ and pneumonia with malaria.⁹ Although regarded as unusual among the newborn and the aged, acute appendicitis has been reported in a sixteen-day-old infant.¹⁰ And with the increase in the life expectancy of the population, more and more cases in the older age groups are encountered.

It is an established surgical principle that the possible complications of acute appendicitis can best be avoided by prompt appendectomy during the early period of the inflammatory process. The favorable influence of the sulfonamides and newer chemotherapeutic agents on the prognosis in the severer forms of acute appendicitis cannot be advanced as a valid argument for temporizing. A short interval from the onset of the symptoms and signs of acute appendicitis is still the optimum time of operation, and this principle cannot be compromised because acute appendicitis may occur during the course of other diseases.

SUMMARY

Ten representative cases of acute appendicitis occurring in the course of other diseases are presented.

The tendency to interpret such cases as possible manifestations of the underlying disease rather than as an independent intraperitoneal lesion is pointed out. The consequences of a temporizing attitude in terms of the increased morbidity of appendiceal peritonitis is discussed.

Acute appendicitis must be diagnosed on the basis of clinical evidence (symptoms and signs) regardless of any coexisting disease.

REFERENCES

1. Rosen S. Otogenous tetanus. *J Mt Sinai Hosp* 8:96, 1941.
2. Medlar, E. M. Extent of variations in the leukocytes of normal individuals. *Am J M Sc* 177:72-87, 1929.
3. Scott, H. W. Jr., and Ware P. F. Acute appendicitis in childhood. *Arch Surg* 50:258-268, 1945.
4. Johnson A. S. Reliability of leukocyte count in diagnosis of appendicitis. *New Eng J Med* 223:373-376, 1940.
5. Twyman R. A., Mussey, R. D., and Stalker L. K. Appendicitis in pregnancy: review of 75 cases. *Proc Staff Meet Mayo Clin* 15:484-487, 1940.
6. Goodman M., and Silverman I. Acute appendicitis in patients with common contagious diseases. *New Eng J Med* 228:533-542, 1943.
7. Metheney, D. and Olson H. H. Appendectomy on poliomyelitis patient in Drinker respirator. *West J Surg* 53:88, 1945.
8. Laipple, T. C. Addison's disease due to cytotoxic contraction of adrenal cortex with sudden death four days after appendectomy. *Ohio State M J* 39:652, 1943.
9. Flowers S. H. Pneumonia malaria appendicitis in one case. *Kentucky M J* 42:143, 1944.
10. Wilson W. E. Appendicitis in newborn: report on case 16 days old. *Proc Roy Soc Med* 38:186, 1945.

ASIATIC SCHISTOSOMIASIS*

Report of an Early Case

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THE following case of acute Asiatic schistosomiasis was unique in that an opportunity was afforded to follow the clinical course with repeated sigmoidoscopies and serial roentgenograms from the onset of symptoms to the termination of a course of treatment—a period of sixty days. More informative accounts of the disease are given by Billings, Winkenwerder and Hunninen,¹ Thomas and Gage,² Faust et al.³ and others.⁴

A 19-year-old soldier of Italian descent was admitted to the 117th Station Hospital on Leyte, Philippine Islands, on December 19, 1945, with a chief complaint of "hives." He stated that about 30 days previously he had been exposed to the infected waters of a tributary of the Palo River and immersed from feet to waist for about 3 hours. He had noticed no swimmers' itch during the next 48 hours and had felt entirely well until the onset of urticaria 2 days before admission. The past history was essentially unremarkable except for an attack of urticaria 5 years previously when the patient had been living in New York City. The family history was negative for allergic diseases.

Physical examination disclosed giant urticarial lesions of the face, torso and extremities. The spleen and liver were just palpable on deep inspiration, and both organs were firm and not tender. The remainder of the physical examination was negative.

During the 1st week in the hospital urticaria was intermittent and associated with angioneurotic edema of the right cheek and infraorbital tissues and the dorsum of the right foot. These lesions cleared after 8 days and did not recur. The white-cell count, which on December 21 was 9850, with 6 per cent eosinophils, on December 26 was 6250, with 10 per cent eosinophils. Sigmoidoscopy on the day after admission showed no nodular lesions of the rectosigmoid region characteristic of schistosomiasis.

On December 24 the temperature, which had been normal, rose to 102°F, with a proportionate elevation of the pulse. Other complaints were anorexia, nausea and moderately severe colicky epigastric pain, which remained troublesome for the next 3 weeks. The temperature and pulse remained intermittently elevated for 24 days, the temperature varying between normal and 103°F, and the pulse between 70 and 120.

On December 25 a dry cough developed and was associated with sibilant rhonchi and a few fine crepitant rales in both lungs. An x-ray film of the chest taken on December 27 showed multiple patches of increased density scattered throughout both lung fields, with increased prominence of the bronchovascular markings.† Concentrated stool specimens on December 31 and January 2, 3 and 4 were guaiac negative. On January 5 a repeated chest plate showed a definite change in the distribution of the areas of increased density.

On January 3 sigmoidoscopy for the first time revealed disease of the rectosigmoid. Several distinctly erythematous areas and erythematous nodular lesions measuring 1 or 2 mm. in diameter were visualized. The nodules did not have the yellow color ascribed to typical lesions of schistosomiasis and did not offer the characteristic resistance with clicking sensation to the lip of the sigmoidoscope. A smear of mucus taken from the surface of one of the nodules was negative

for ova. Concentrated stool specimens were negative for ova on January 5 and 7. Cysts of *Entamoeba histolytica*, however, were found on the latter date and again on January 8. Sigmoidoscopy was repeated on January 9, and ten to twelve nodular lesions, similar to those previously observed, were visualized in the same region of the rectosigmoid. The nodules, which were more prominent and offered resistance to the lip of the sigmoidoscope in the typical fashion, were still red. A few pinpoint erythematous lesions were considered typical of amebiasis. A biopsy specimen of one of the nodules was negative on direct examination, probably because a deep enough bite had not been taken.

In the meantime, the patient was running a fever, complaining of severe pains in the upper abdomen and right upper quadrant. There was some increased tenderness of the liver edge to palpation, and the area of liver dullness had become tender to light percussion. On January 7 the white-cell count was 20,150, with 64 per cent neutrophils, 14 per cent eosinophils and 22 per cent lymphocytes. Although a diagnosis of schistosomiasis japonica seemed likely, it was considered advisable, in the lack of definite proof, to try a 6-day course of emetine hydrochloride to evaluate the effect of amebic infection on the liver symptoms and the fever. There was no response of temperature or symptoms to emetine. A chest plate on January 11 showed some increase in the patchy nodular lesions in both lung fields without significant change in the bronchovascular markings.

On January 14 sigmoidoscopy was repeated, and the nodules for the first time had a distinctly yellowish or whitish-yellow color, a narrow erythematous base being observed in some of them. With the use of a more suitable biopsy forceps one of the nodules was excised and examined microscopically in a drop of saline. Clusters of ova of *Schistosoma japonicum* were seen. Examination of the blood showed a red-cell count of 4,900,000, with a hemoglobin of 14 gm (Sahli), and a white-cell count of 35,000, with 40 per cent eosinophils.

On January 15 a course of antimony potassium tartrate was begun. A fresh 1 per cent aqueous solution was prepared on each day of treatment and within ½ hour prior to injection, 0.5 gm of the drug being dissolved in 50 cc of sterile distilled water under aseptic precautions, no attempt was made to sterilize the solution after it had been prepared. From this solution the appropriate dose was withdrawn and incorporated in 1000 cc of 5 per cent dextrose in physiologic saline, for slowness of injection and a reduction of local irritating effects. The drug was given on alternate days, beginning with 40 mg (representing 4 cc of the 1 per cent solution) and increasing the dose by 20 mg each time until 140 mg (14 cc) had been reached, this dose was not exceeded for the remainder of the course. A total of 18 gm was given in fifteen injections over a period of 31 days. It was considered advisable to postpone the twelfth injection because of rather severe upper abdominal pains on the preceding day. Instructions had been left with the nursing staff to discontinue the intravenous injections if nausea, vomiting, upper abdominal pain, a sense of constriction or pain in the chest, stiffness of the muscles, bradycardia or a drop in the blood pressure occurred. One and a half hours were allowed for the intravenous injection, and the patient was kept in bed for 1 hour after each treatment. Physical examinations were made daily, blood pressures were taken twice a day, the urine was examined every other day and electrocardiograms were taken once a week at another hospital. Fluids were forced to prevent possible kidney damage from the drug, and the intake and output were recorded. A high-carbohydrate, high-protein diet with added vitamins was given to guard against liver damage. No serious toxic reactions were observed.

Clinically, improvement began early. After the second injection the temperature became normal and remained so thereafter except for a transient elevation from an upper

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‡Reproductions of this and subsequent roentgenograms will be included in the reprints of this paper.—Ed.

respiratory infection. The appetite improved gradually, and the weight lost in the early part of the illness was regained. Only one positive stool was reported, and this was obtained on the day after the first dose of antimony potassium tartrate. On this occasion numerous ova were seen, consisting generally of mature forms containing actively motile miracidia. The spleen and liver were no longer palpable after January 29. A chest plate on February 16 showed less infiltration in both lung fields, although the hilar markings were still accentuated to the same extent as before. The white-cell counts on January 26 and 29 were respectively 20,550, with 40 per cent eosinophils, and 11,000, with 43 per cent eosinophils, whereas on February 4, 8 and 14 they were 9000, with 60 per cent eosinophils, 12,800, with 31 per cent eosinophils, and 7300, with 30 per cent eosinophils. Sigmoidoscopic evidences of improvement began as early as February 1, and by February 15 there was still further improvement, so that the nodules might readily have been missed had their previous location not been known. On February 16 the patient was transferred, greatly improved, to a general hospital for evacuation to the United States.

DISCUSSION

Several features of this case deserve comment. In the first place, the failure of laboratory tests to demonstrate ova in the stools is not infrequent, in spite of refined concentration technics. Only one positive stool specimen was obtained during the patient's hospitalization, and that on the day following the first dose of antimony potassium tartrate, when the stool became heavily laden with ova. This may have been simple coincidence, but was more probably due to the provocative action of the drug on the gravid female worms, causing them to expel their eggs at one time. A somewhat analogous reaction is seen in malarial infections, in which the blood smear may not become positive until after a dose of quinacrine (Atabrine), when a heavy infection may become manifest.

Sigmoidoscopy has received attention as providing valuable diagnostic aid following a report by Johnson and Berry⁵ that yellowish nodules of the upper rectal and rectosigmoid mucosa were characteristic of Asiatic schistosomiasis. From these nodules or pseudotubercles, which occur singly or in clusters, nests of ova can be removed with a simple biopsy forceps. Although we were aware of this diagnostic feature the diagnosis was not made because at first no pseudotubercles could be found and subsequently small, red macules and elevated lesions were observed from which no ova could be obtained. So far as we know, this is the first reference to the initial appearance of the yellow nodules of Johnson and Berry, with the lapse of eleven days, however, there was no mistaking their nature—the greater elevation, sense of firmness to the tip of the sigmoidoscope and yellowish color were all characteristic, and biopsy findings at this stage were merely confirmatory.

The serial roentgenograms of the chest were also interesting. Such films are not in themselves pathognomonic, presenting the picture of bronchopneumonia, but their association with urticaria, angioneurotic edema, leukocytosis, eosinophilia, fever and abdominal pain with liver tenderness should be

considered strongly suggestive of schistosomiasis and should point to the advisability of repeated examinations of the stools and sigmoidoscopy. The pulmonary infiltrations have a doubtful pathogenesis. It is not known whether the roentgenologic picture represents a reaction of the lung parenchyma to ova transported from the mesenteric venules via the portal circulation and liver or to adult worms living in the lungs or to their ova deposited there. In fatal cases of Egyptian schistosomiasis with pulmonary involvement, adult worms have been found in the arteries of the lungs. It would not be at all surprising if adult worms of *S. japonicum* also develop in the lungs and that the eggs when present are the product of the worms located there. In this respect it is interesting to note that the same problem arises to explain the nature of cerebral schistosomiasis, in which ova have thus far been found only in the brain substance, with no evidence of the presence of adult worms.⁶

Attention is called to the complete lack of effect of 0.4 gm of emetine given for six days. The drug was administered because of the possibility that some of the symptoms were due to an amebic hepatitis, although it was not expected to be of great value. Older authorities had stated that the drug had some schistosomicidal effect, but none was demonstrated with the small amount used in this patient. In marked contrast was the gratifying symptomatic and objective response to antimony potassium tartrate. Although two potential myocardial depressants were used in this case, no evidences of cardiac damage were detected.

SUMMARY

An early case of Asiatic schistosomiasis is reported.

The characteristic yellowish nodules of the rectosigmoid and upper rectum were shown to have an earlier stage in which they have a distinctly red color and are smaller and less resistant to the sigmoidoscope than they are in the later course of their development. The diagnostic value of sigmoidoscopy is confirmed.

Serial roentgenologic findings are presented that may have represented a reaction of the lung parenchyma to ova or adult worms of *Schistosoma japonicum*.

The effectiveness of antimony potassium tartrate (tartar emetic) in this case was demonstrated.

REFERENCES

- 1 Billings F T, Winkenwerder, W L, and Hunninen A V. Studies on acute schistosomiasis japonica in Philippine Islands. I. Clinical study of 337 cases with preliminary report on results of treatment with iodoquin in 110 cases. *Bull. Johns Hopkins Hosp* 78:21-56, 1946.
- 2 Thomas, H M, Jr, and Gage, D F. Symptomatology of early schistosomiasis japonica. *Bull U S Army M Dept* 4:197-201, 1945.
- 3 Faust, E C, Wright W H., McMullen, D B, and Hunter G W. Diagnosis of schistosomiasis japonica. I. Symptoms, signs and physical findings of schistosomiasis japonica at different stages in development of disease. *Am J Trop Med* 26:4:273-276, 1945.
- 4 Schistosomiasis japonica. *Bull U S Army M Dept* 4:273-276, 1945.
- 5 Johnson A S Jr and Berry, M G. Aid in recognition of schistosomiasis japonica. *Bull U S Army M Dept* 4:125, 1945.
- 6 Carroll D G. Cerebral involvement in schistosomiasis japonica. *Bull Johns Hopkins Hosp* 78:219-234, 1946.

MEDICAL PROGRESS

THE PHYSIOLOGIC AND CLINICAL SIGNIFICANCE OF PLASMA PROTEINS AND PROTEIN METABOLITES*

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PROTEIN is an essential component of protoplasm. Both structure and function of body tissues are dependent on specific proteins, such as enzymes and hormones. Fluid balance, hemostasis, many hormone and lipoprotein complexes and certain immune mechanisms are related to protein nutrition. Recent observations derived from many sources have re-emphasized and extended the clinical significance of plasma proteins, protein metabolites and protein degradation products. The concept of constant interchange or "dynamic equilibrium" between the proteins of blood and other tissues,^{1,2} the elucidation of indispensable amino acids,^{3,4} the application of heavy nitrogen and marked carbon to problems of nitrogen metabolism and immunology⁵⁻⁷ and the adaptation of physico-chemical technics — for example, electrophoresis — and fractionation procedures to plasma proteins⁸⁻¹¹ are fundamental contributions to better clinical understanding of plasma protein significance. The significance, characterization and function of various circulating plasma proteins and protein metabolites, the evaluation of protein abnormalities and the general interrelations of amino acids, protein synthesis and nitrogen metabolism are considered in this paper.

CIRCULATING PROTEINS

The modern technic of electrophoresis, as developed by Tiselius,⁸ affords a means of characterizing plasma proteins. This procedure depends on the application of an external electric field of force to charged protein molecules dissolved in a suitable solvent. Under such conditions, proteins move in one direction in acid solutions and in the opposite direction in alkaline solutions. Thus, in an apparatus providing a given electromotive field strength acting on proteins dispersed in a salt solution, movement of the protein is determined by its physical properties and the hydrogen ion concentration, the molar concentration and the nature of the solvent. Since different components of a protein aggregate usually move with different velocities, it is possible to distinguish several components within a com-

plex protein aggregate such as plasma. Specialized refractometric optical systems, which project a shadow (*Schlieren*) pattern of the migrating protein on a photographic screen, afford a permanent record of electrophoretic mobility. Both the characteristic rate of motion, which determines the probable protein component, and the apparent relative concentration of that component may be calculated from the *Schlieren* pattern.¹²

Analyses of human plasma by modifications of this method have postulated at least six electrophoretic components: albumin, alpha-1, alpha-2, beta and gamma globulin and fibrinogen.¹²⁻¹⁶ (Fig. 1) Fractionation studies have indicated their distribution in plasma (Table 1). The conventional sodium sulfate "salting out" method of Howe,²¹ which precipitates fibrinogen, euglobulin and pseudoglobulins I and II at increasing molar concentrations, affords a somewhat different distribution (Table 1). Similarly, other methods, including ultracentrifugal sedimentation, osmotic pressure and viscosity, that depend on heterogeneous physical and chemical properties of protein, such as size, shape and electrical charge, provide diverse plasma protein distributions. Determination of plasma protein components by electrophoresis differs from the more familiar chemical method in yielding more complete fractional resolution, which particularly minimizes the overlap of albumin and the various globulins. Sodium sulfate fractionation, for example, appears to assign approximately 5 per cent more nitrogen (31 per cent more protein) to the albumin fraction than indicated by electrophoretic technics.²² Accordingly, electrophoretic albumin-globulin ratios tend to be lower, (about 30 per cent) than the chemically determined equivalent.¹⁶ The more precise data from electrophoretic analyses of plasma should provide a supplemental, somewhat more readily interpreted, body of experimental and clinical findings. Extensive data derived from electrophoretic analyses of plasma in health and disease are rapidly becoming available.

Alterations in plasma protein concentration with age, sex, race, health and disease are well known. Normal ranges^{18, 19, 23, 24} are denoted in Table 2. Deviation from these values occurs in many diseases. Hypoproteinemia, usually reflecting a depletion of the albumin fraction, is more frequent clinically than hyperproteinemia, which usually represents

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an increase in one or several of the globulin components of plasma. Diseases in which hypoproteinemia or hyperproteinemia may occur are listed in Table 3.

The clinical significance attending alterations in each of the various plasma protein fractions is not completely clear. Some pertinent observations, however, have been made.

Serum albumin is the most important circulating protein for maintenance of colloid osmotic (oncotic) pressure of the blood. Constituting approximately 55 to 60 per cent* of plasma protein, it is responsible

appears to increase in relation to plasma volume and surface area until maximal values are approximated coincident with puberty (see Tables 2 and 5). Decreased serum albumin is most frequently the result of protein loss by leakage into extravascular spaces (trauma or shock, or both) into urine (nephrosis, chronic glomerulonephritis and so forth) or from wound surfaces (hemorrhage and burns), inadequate protein synthesis associated with extensive liver damage (cirrhosis or hepatitis) or altered hepatic function (concomitant to severe anemia, chronic nephritides, various infections and so forth), inade-

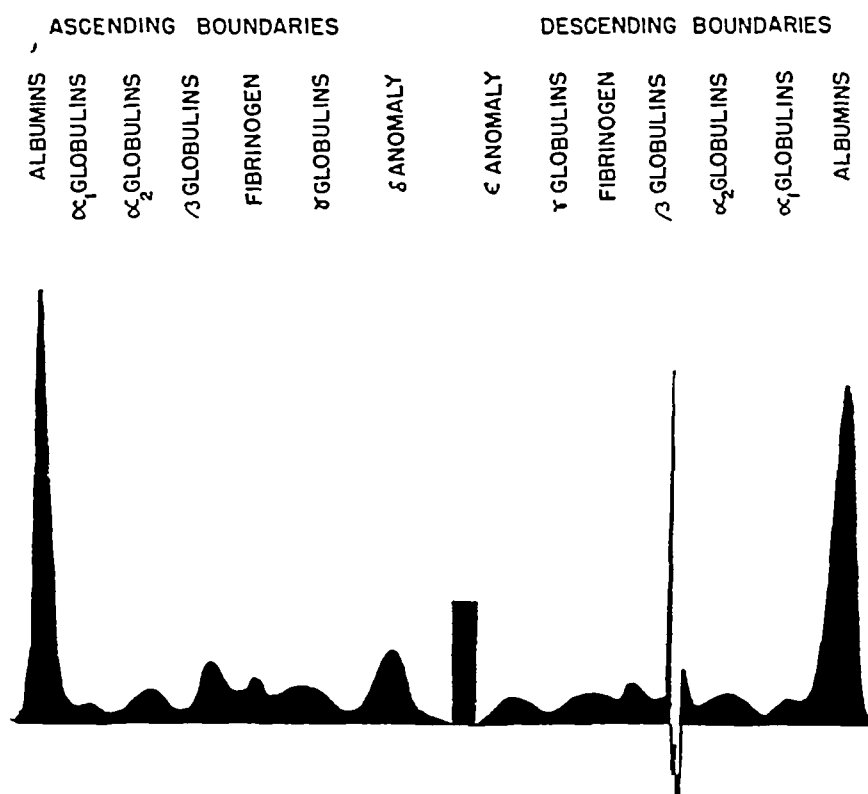


FIGURE 1 A Typical Electrophoretic Pattern of Human Plasma

This diagram was derived from analysis of a 2 per cent solution of pooled normal human plasma in a sodium diethyl barbiturate buffer (pH 8.6) and an ionic strength of 0.1. It was kindly furnished by Dr S. H. Armstrong, Jr., of the Department of Physical Chemistry, Harvard University.

for about 80 per cent of the oncotic pressure.²⁷ Its small size (molecular weight, 70,000) and relatively larger net charge account for an osmotic effect greater than that exerted by combinations of the various globulins (molecular weight, approximately 170,000 to 180,000). Serum albumin apparently attains maximal (adult) concentration at approximately one year of age^{18, 24}; electrophoretically observed albumin concentrations of maternal and fetal plasmas, however, appear to be similar.²⁵ The quantity of circulating protein, including albumin, ap-

*Present estimates are somewhat lower: 52 to 55 per cent.

quate dietary protein intake, and increased utilization or decreased absorption of protein. Increased protein utilization occurs when metabolism requires burning of protein for energy if supplies of carbohydrate and fat are inadequate to support caloric needs. This may ensue when parenteral amino acids, plasma and electrolyte replacement therapy are administered without supplying caloric requirements in the form of glucose or fat, when increased protein and caloric demands are not met in various acute and chronic diseases, such as typhoid fever, hepatitis, tuberculosis and hyperthyroidism, or

when the heightened metabolic demands of rapid growth, pregnancy and lactation are confronted with relative protein and caloric inadequacy. Decreased absorption of protein is primarily associated with gastrointestinal abnormalities, including diarrhea, specific mucosal or intestinal vascular disease and surgical stomas of the small bowel.

Depletion of plasma protein, — specifically, albumin, — usually associated with a decreased plasma volume, probably represents a much more extensive depletion of tissue protein^{1, 34, 35}. Thus, reversal of hypoalbuminemia with associated replenishment of tissue protein understandably requires consider-

The albumin fraction appears to serve other functions of clinical interest. Partial binding of the sulfonamide drugs to albumin may account for their distribution in body fluids, solubility in plasma and decreased bacteriostatic activity³⁷. The dye T-1824, used in the clinical determination of blood volume, is bound by albumin and migrates with it in the electrophoretic field. Its disappearance from plasma appears to be related to the rate at which albumin escapes³⁸. It has been reported that normal or abnormally occurring albumin fractions may inhibit the colloidal gold reaction,^{39, 40} cephalin-cholesterol flocculation⁴¹ and sedimentation rate⁴². Subsequent

TABLE 1 *Distribution of Human Plasma Protein Components in Normal Adults as Determined by Electrophoretic and Sodium Sulfate Fractionation*

ELECTROPHORETIC FRACTIONATION*			SODIUM SULFATE FRACTIONATION		
COMPONENT	PERCENTAGE OF TOTAL PROTEIN†	CONCENTRATION gm./100 cc	COMPONENT	PERCENTAGE OF TOTAL PROTEIN†	CONCENTRATION‡ gm./100 cc
Total protein		6.03-6.72	Total protein		6.0-8.0
Albumin	55	3.32-4.01	Albumin	67	4.1-5.0
Globulin					
Alpha 1	5	0.31-0.32	Pseudoglobulin II	7	0.2-0.8§
Alpha 2	9	0.48-0.52			
Beta	13	0.78-0.81	Pseudoglobulin I	19	0.8-1.9§
Gamma	11	0.66-0.74	Euglobulin	4	0.1-0.4§
Fibrinogen	7	0.34-0.43	Fibrinogen	3	0.17-0.25
Total	45	2.71-2.72	Total globulin	33	1.9-3.3

*The distribution of components in normal pooled human plasma as derived from electrophoretic analysis is based on the total refractive increment contributed by each component. The quantitative amount of each fraction is based on nitrogen analysis assuming the conventional conversion factor of 6.25. A further assumption tentatively assigns a similar refractive increment per gram of nitrogen to all components.¹¹ Data derived from several studies.^{9, 11, 16, 17} Fractionation in diethylbarbiturate buffer at pH 8.6.

†Percentage of total protein represents an approximation.

‡Data derived largely from Trevorrow et al.¹⁶ and Millam.¹⁹

§Data from Cantarow and Trumper.²⁰

able quantities of protein or albumin. With sufficient reduction of serum albumin and resultant diminution of plasma oncotic pressure, edema is likely to occur. The occurrence of edema, however, is modified by hydration, electrolyte (particularly sodium) concentration, tissue pressure, lymph flow, capillary permeability, extracellular fluid pressure, adrenocortical and gonadotropic hormones and so forth. It has been stated that the critical plasma concentrations below which edema occurs is approximated by a total protein of 5.5 gm per 100 cc, an albumin level of 2.5 gm per 100 cc and a plasma specific gravity of 1.023.³⁶ Clinical aberrations from this observation are numerous, as might be expected, since protein concentration measurements afford an inadequate indication of the oncotic effect exerted by the total circulating protein and many associated factors further modify the occurrence of clinical edema. Recent evidence questions the validity of Starling's generally accepted oncotic equilibrium theory and suggests the inadequacy of a simple hypoproteinemic causation of such a well known clinical entity as famine edema.³⁶

unpublished data on fractionation have put these activities in small alpha-1 globulin impurities.⁴⁴

Albumin, as a product of plasma fractionation, has considerable clinical value in the therapy of hemorrhagic, traumatic or burn shock.⁴⁴⁻⁴⁶ It is chiefly useful in rapidly restoring the diminished plasma volume toward normal at the expense of extravascular fluids.⁴⁷ Albumin has also seemed efficacious in the treatment of severe malnutritional hypoproteinemia occurring in adults⁴⁴ and infants,⁴⁵ in nephritis^{17, 48} and in cirrhosis.⁵⁰

Hyperproteinemia, not the result of decreased plasma volume, is usually synonymous with hyperglobulinemia — an increase in one or several globulin fractions. Extensive data pertaining to alterations in the various electrophoretic globulin fractions are not yet available. Globulins have been reported to attain maximal (adult) concentrations by the fourth year of life.¹⁸ Alpha-1 globulin may be closely associated clinically with the electrophoretically appositional albumin, since it appears to exert a similar effect on oncotic pressure⁵¹ and to resemble albumin in its plasma clearance.⁴⁹ Alpha-1 and alpha-2

globulins occur in lower concentrations in fetal than in maternal plasmas.²⁵ Increased alpha globulins have been reported in a variety of diseases^{7, 49, 50, 52-55}. The significance of these observations is unknown. It has been suggested that the depletion of plasma albumin may be reflected by a compensatory increase of alpha globulin in liver disease,⁵² malnutrition, tuberculosis and carcinoma⁵⁶ or, conversely, that hyperglobulinemia prompts an equilibrium fall in albumin.⁵⁷

Beta globulins are carriers of lipid components and, with the alpha globulins, constitute the lipoproteins of plasma.^{12, 58} Approximately two thirds of the total plasma cholesterol appears to be asso-

Relatively purified plasma fractions composed largely of beta and gamma globulins have been prepared as specific isohemagglutinins with anti-A and anti-B activity.⁶² These fractions have been found clinically acceptable as standardized blood-grouping serums.⁶²

Since immunologic mechanisms are partially dependent on antibody response and many antibodies are related to gamma globulin, considerable interest has centered about electrophoretic demonstrations of relative changes in the gamma-globulin fraction of plasma. Antibodies reacting with diphtheria toxin, streptococcal erythrogenic toxin, influenza A virus, mumps virus and the H antigen of *Eberthella*

TABLE 2 Normal Plasma Protein Concentration Values from Birth to Maturity

Age*	PLASMA PROTEIN†			
	TOTAL PROTEIN gm/100 cc	ALBUMIN‡ gm/100 cc	GLOBULIN gm/100 cc	FIBRINOGEN gm/100 cc
Premature infants ⁴	4.55 ± 0.59	5.5 ± 0.65	1.01 ± 0.4	0.27 ± 0.15
Full-term infants ^{16, 24}	5.11 ± 0.76	7.6 ± 0.4	1.34 ± 0.41	0.24 ± 0.04
	to 5.70 ± 0.45	to 7.9 ± 0.5	to 1.66 ± 0.29	to 0.23 ± —
Birth to 1 year ²⁴	6.10 ± 0.29	4.97 ± 0.73‡	1.38 ± 0.68	0.28 ± 0.08‡
1-4 years ¹⁸	6.94 ± 0.47‡	4.59 ± 0.31	2.03 ± 0.34‡	0.21 ± 0.06
	to 4.83 ± 0.30	to 5.0 ± 0.78	to 2.4 ± 0.74	to 0.28 ± 0.04
5-12 years ²⁴	7.30 ± 0.59	5.0 ± 0.78	2.4 ± 0.74	0.28 ± 0.04
Under 15 years ¹⁹	7.16	4.72	2.49	Included with globulin
Adults ^{18, 19}	7.18 ± 0.01‡	4.59 ± 0.011	2.54 ± 0.1‡	—
	to 6.94 ± 0.47	to 4.70 ± 0.32	to 2.03 ± 0.34	to 0.21 ± 0.06
Adult range (95 per cent) ¹⁹	6.3 — 8.0	3.9 — 5.3	1.3 — 3.4	Included with globulin

*No significant variation with sex, but some racial variation

†Values obtained are somewhat variable depending on technique of determination. Most of the reported total protein values are derived from micro-Kjeldahl analyses, and the albumin and globulin from sodium sulfate fractionation.

‡Albumin may vary somewhat with the season. The variation may be a manifestation of seasonal blood volume changes.¹⁸

§Indicates mature level attained

ciated with beta globulin. Over half the carotene and phospholipids are also concentrated with the alpha and beta globulin fractions. Prothrombin appears to be a beta globulin.¹² The thymol-turbidity reaction appears to be related to alpha and beta globulins.⁴¹

Demonstrable increases in beta-globulin components of plasma have been reported in association with several diseases^{13, 14, 17, 49, 50, 52-56, 58-61} and in maternal plasma at parturition.²⁸ The observed increase appears to depend on abnormally large amounts of lipoids, which migrate with the beta and alpha fractions. The refractometric error introduced by the plasma lipoids in such diseases subjects calculation of the plasma concentration of a given electrophoretic protein component to considerable error.⁶⁰

typhosa have been immunologically demonstrated in the gamma-globulin fraction.⁶⁴ The concentration of these antibodies was some fifteen to thirty times that in pooled plasma. All antibodies, however, are not contained in the gamma-globulin fraction of plasma. The O antibody of *E. typhosa*, for example, appears to be associated electrophoretically with beta and possibly alpha, as well as with gamma globulin. Similarly, all gamma globulin is not antibody.⁶⁵ The presence of antibodies⁶⁶ and normal serum gamma globulin in lymphocytes⁶⁷ indirectly supports the concept of the extrahepatic origin of globulin. Antibody release from lymphocytes, attended by an increased serum gamma globulin, may be mediated through pituitary-adrenocortical control.⁶⁸

Clinical evidence pertaining to the change in gamma globulin is somewhat less striking than inference from immunologic data suggests. In relation to infant immunity it is interesting that the gamma-globulin concentration of fetal plasma, determined from placental blood at birth, is considerably greater than that occurring in the parenteral maternal plasma.²⁸ Gamma globulin has been

to that of gamma globulin.⁷⁰ Gamma globulin may be diminished in chronic malnutrition associated with hypoproteinemia.^{56, 71} This observation is particularly interesting in view of the possible relation of protein deficiency to impaired antibody production.⁷² Gamma globulin appears to be largely responsible for positive colloidal gold and cephalin-flocculation tests.⁴⁰ It has no effect on the thymol-

TABLE 3 Conditions Associated with Alterations in Plasma Protein Concentration *

HIGH CONCENTRATIONS		LOW CONCENTRATIONS	
General		General	
Usually associated with dehydration and with increased globulin which are frequent in diseases of reticuloendothelial system and in chronic infections		Usually associated with mechanical loss of protein by extravasation or renal excretion or with decreased albumin formation as result of malnutrition or liver disease	
Specific		Specific	
Dehydration		Physical loss of plasma proteins from circulation	
Insufficient fluid intake		Hemorrhage acute or chronic and blood dyscrasias	
Fluid loss		Weeping wounds or skin lesions (burns)	
Intestinal obstruction and fistulas		Shock surgical and traumatic	
Diarrhea especially in infants and also cholera and dysentery		Kidney disease with albuminuria	
Vomiting		Nephrosis	
Severe diabetic acidosis		Chronic glomerulonephritis	
Intense heat and exertion		Amyloidosis	
Addison's disease			
Shock, surgical and traumatic		Malnutrition (low albumin)	
Burns, first few hours (in some cases)		Dietary inadequacy in chronic infections	
Pulminant infections		Low-protein diet	
Diseases involving reticuloendothelial system (high globulin)		Incomplete absorption, as in sprue and celiac syndrome	
Multiple myeloma		Cancer of stomach and pancreas	
Leukemia		Pernicious anemia	
Liver cirrhosis and cancer		Diabetes mellitus unregulated	
Acute hepatitis		Hyperthyroidism	
		Toxemia of pregnancy	
Chronic infections (high globulin)			
Acute nephritis		Conditions with retarded albumin synthesis presumably because of liver damage (low albumin)	
Ulcerative tuberculosis		Cirrhosis and cancer of liver	
Syphilis		Chronic poisoning (benzene phosphorus and so forth)	
Lymphopathia venereum		Hepatitis, chronic	
Subacute bacterial endocarditis		Hepatorenal syndrome	
Acute disseminated lupus erythematosus			
Periarteritis nodosa			
Rheumatic fever			
Rheumatoid arthritis			
Boeck's sarcoid			
Leprosy			
Kala-azar			
Schistosomiasis			
Filariasis			
Trypanosomiasis			
Chronic suppurative infections			
Pyelonephritis			
Pyonephrosis			
Gangrene associated with diabetes mellitus			
Malaria			
Tuberculosis			

*Modified from Kagan²⁵ and from Phillips et al.²⁶

reported as increased in scarlet fever — the increase appearing to be associated with increased titer of antistreptolysin O³⁴ — and in relapsing malarial infection with *Plasmodium vivax* associated with paroxysms.⁵³ An increase in this fraction has also been noted in association with acute nephritis, acute rheumatic fever, periarteritis nodosa,^{17, 55} lupus erythematosus⁵⁹ and various subacute and chronic infections.⁵⁵ A nonspecific increase in gamma globulin has been observed in various types of myeloma^{13, 55} and chronic hepatic disease.^{50, 52, 55} The Wassermann antibody appears to be associated with the gamma-globulin fraction, having an electrophoretic mobility between beta and gamma components and a sedimentation constant similar

turbidity reaction,⁴¹ and may inhibit the sedimentation rate,⁴² although in particular cases an accelerated sedimentation rate is apparently related to gamma-globulin increase.⁵⁵

The clinical administration of relatively purified gamma globulin has proved efficacious in the prevention and attenuation of measles^{73, 74} and in the prophylaxis of infectious hepatitis^{75, 76} and mumps orchitis (if the gamma globulin is derived from mumps convalescent serums).⁷⁷

Fibrinogen, the last of the currently isolated major plasma protein components, appears to undergo little fluctuation with growth and health.¹⁸ It is primarily concerned with the blood-clotting mechanism. Fibrin has been isolated, purified and

adapted to clinical use^{9, 12} Fibrinogen concentrations may be increased in a variety of conditions acute infections, malaria, pregnancy and menstruation and following roentgen irradiation,⁷⁸ nephrosis and cirrhosis^{17, 50, 55} Presumably, a relatively large proportion of protein* having an electrophoretic mobility similar to fibrinogen is a beta globulin not

several of the globulin fractions⁵⁵ Decreased plasma fibrinogen has been reported in association with several diseases, but normal concentrations are low and variations are large, hence, the deviations are difficult to interpret Sodium sulfate precipitation of fibrinogen, generally used, may precipitate some of the fibrinogen with globulin and may further

TABLE 4 Characterization, Known Physiologic Function and Reported Electrophoretic Variations with Disease of the Major Plasma Protein Components*

DATA	ALBUMIN	ALPHA GLOBULINS	BETA GLOBULIN	GAMMA GLOBULIN	FIBRINOGEN
Occurrence in plasma fractions†	Fraction V (98.5-100%)	Fraction IV (64%) Fraction III (21%)	Fraction III (61%) Fraction IV (31%)	Fraction II (98-99%)	Fraction I (62%)
Other known factors in fraction†		Iron-binding globulin, serum esterase hyper-tensinogen vitamin A carotenoids cholesterol phosphatides estrogens isoagglutinins complement C ₁ luteinizing follicle stimulating and thyrotropic hormones protein-bound iodine and alkaline phosphatase			Antihemophilic globulin
Known physiologic function	Maintains oncotic pressure of blood maintains plasma volume binds sulfonamide and dye T-1824 inhibits sedimentation rate of red cells	Constitute lipoproteins of plasma Alpha I globulin has oncotic effect and plasma clearance similar to that of albumin impurities associated with it appear to inhibit cephalin-cholesterol and colloidal gold flocculation	Principal component of Bence-Jones protein largely responsible for thymol flocculation reaction related to prothrombin	Comprises antibodies for diphtheria toxin streptococcus erythro-genic toxin and influenza A virus and H antigen of <i>E. typhosa</i> associated with Wassermann antibody occurs in lymphocytes largely responsible for colloidal gold and cephalin-flocculation reactions inhibits sedimentation rate of red cells	Fibrinogen in blood-coagulation mechanism largely responsible for rapid sedimentation rate of red cells
Reported alterations in several diseases					
Increased		Nephrosis‡ Cirrhosis‡ Arsenical hepatitis with low albumin‡ Scarlet fever Malnutrition Tuberculosis‡ Diabetes mellitus	Nephrotic syndrome Cirrhosis Metastatic carcinoma of liver Multiple myeloma May be associated with increased serum cholesterol	Normal fetal plasma Cirrhosis Multiple myeloma Acute nephritis Periarteritis nodosa Lupus erythematosus Relapsing (P. ricax) malaria Addison's disease Monocytic leukemia Acute rheumatic fever Associated with anti-streptolysin-O titer in scarlet fever	Nephrosis Hepatic cirrhosis Relapsing P. ricax malaria Pregnancy
Decreased	Malnutrition with hypoproteinemia Hepatic cirrhosis Extensive metastatic hepatic carcinoma Chronic glomerulonephritis with albuminuria or nephrotic syndrome Relapsing P. ricax malaria Chronic tuberculosis			May be diminished in nephrotic syndrome Malnutrition with hypoproteinemia	

*Data pertaining to physiologic function and abnormal variations of the specific plasma protein components are at present, quite limited Subsequent data will undoubtedly extend clarify or modify those indicated in this table

†The concentration of the principal protein components in the various fractions denoted as percentages is derived largely from data of Cohn and Strong Hughes, and Armstrong¹² and subsequent reports from the Department of Physical Chemistry Harvard Medical School Fractions denoted by Roman numerals refer to that portion of the plasma protein precipitated from an alcohol-water solution of known concentration ionic strength and pH at very low temperatures The precipitates are subsequently dried, purified and analyzed for protein components by electrophoretic techniques Several electrophoretic components may be concentrated in any one fraction Six major fractions (I-VI) and seven subfractions have been evolved by various procedures to date Fractions II and III are precipitated together in several methods

‡Many of the factors that appear to be concentrated in Fraction II plus III have not been specifically isolated or purified others as yet undemonstrated, may occur in these or other fractions

§The increase is represented largely by alpha-2 globulin

specifically related to the blood-clotting function¹¹ The sedimentation rate of erythrocytes may be related to fibrinogen,⁴² presumably being proportional to the amount of so-called "contractinogen" it contains⁷⁹ Recent evidence, however, suggests that the elevated sedimentation rate occurring in many conditions may also be related to one or

impair interpretation¹⁸ Reported physiologic functions of the plasma protein components and electrophoretic variations occurring in association with several diseases are summarized in Table 4

Observations pertaining to pathologic variations in albumin and globulin have repeatedly indicated that numerical expression of the albumin-globulin

ratio provides little insight into specific alterations in albumin or globulin fractions^{18, 24, 26, 80} Used as a diagnostic aid, the ratio may be quite misleading in nephrosis, a decreased albumin-globulin ratio is dependent on depleted albumin and probable, relative increases in alpha and beta globulins, and in cirrhosis, on depleted albumin, increased fibrinogen and gamma globulin, in malnutrition, it probably depends on depleted albumin and relatively increased alpha globulin, in pregnancy it may be dependent on hemodilution of albumin, with a relative increase in fibrinogen, and in chronic infections, it depends on an unchanged albumin and increased beta-globulin and gamma-globulin frac-

volume^{34, 83-86} Thus, a protein concentration of 6 gm per 100 cc in a patient with a total plasma volume of 2000 cc represents a significantly different amount of circulating protein than that occurring in another person of similar size, also with a total protein of 6 gm per 100 cc but a plasma volume of 1000 cc Such a hypothetical case indicates a difference of 60 gm (50 per cent) in the total circulating plasma protein This difference is masked by the relatively unphysiologic consideration of concentration alone — for as Peters⁸⁰ has pointed out, a three-dimensional function cannot be evaluated by two-dimensional measurements, and alter-

TABLE 5 Normal Plasma Volume* and Circulating Protein Values from Birth to Maturity

Age† yr	PLASMA VOLUME			CIRCULATING PROTEIN‡	
	TOTAL cc	PER KILOGRAM cc	PER SQUARE METER cc	TOTAL§ gm	UNIT gm /unit of plasma volume
Neonatal ²⁰	156 (144-164)	48 (44-55)	740 (660-800)	8 (7-10)	39 (35-43)
Under 1 ²⁰	203 (144-270)	43 (28-55)	747 (600-940)	12 (8-18)	46 (37-58)
1-4 ²⁰	577 (483-653)	41 (34-46)	942 (825-1020)	40 (34-46)	66 (57-71)
5-12 ²⁰	1146 (891-1590)	41 (37-46)	1120 (1010-1230)	84 (65-116)	84 (74-90)
13-16 ²⁰	2230 (2030-2610)	42 (34-52)	1450 (1195-1710)	160 (146-186)	104 (86-123)
17-89 ²⁰⁻²³	2800 (2300-3100)	44 (40-49)	1628 (1624-1680)	196 (162-220)	114 (113-118)

*As determined with azo dye T-1824 (Evans blue)

†All children within anthropometric norms

‡Total circulating protein values derived from average plasma volume data and average plasma protein concentrations noted in Table 2 tabulated values are averages and do not include standard deviations

§Total circulating protein = total protein (gm per 100 cc.) — 100 x total plasma volume (cc)

tions Albumin is synthesized principally in the liver, whereas globulin may be synthesized extra-hepatically^{67, 81} The amino acid compositions of albumin, gamma globulin, beta globulin and fibrinogen differ⁸² Since the origin, structure and function of albumin and globulin differ and the various globulin fractions have further structural and functional differences, it is evident that these fractions, determined with total protein concentrations, should be considered individual variables The albumin-globulin ratio, therefore, as generally used has little significance and frequently leads to confused clinical interpretations

Hypoproteinemia and hyperproteinemia, by usage, refer to the quantity of protein dissolved in an arbitrary amount of plasma Since the volume of circulating plasma is subject to considerable change in relation to growth, health and acute and chronic disease, it is evident that significant changes in quantities of circulating plasma protein may be masked if the protein concentration is measured without regard for expanding or contracting blood

tions in total circulating protein and plasma volume cannot be estimated accurately from total protein concentrations^{85, 86}

Plasma-volume alterations are not static phenomena As a phase of the total extracellular compartment, plasma-volume change is subsequent to factors altering water balance Changes in plasma volume have a temporal significance — for example, *relative* to the previously existing plasma volume in a given patient or *absolute* in regard to a previously normal plasma volume Altered concentrations of circulating plasma components may be masked by either an increased or a decreased plasma volume Plasma protein and electrolyte concentrations, therefore, may be more relative than absolute An increased plasma volume is most frequently dependent on one or several factors altered renal function or sodium retention, or both, increased plasma bicarbonate, with altered carbon dioxide and oxygen tensions, and an increased basal metabolic rate, and decreased circulating cell volume

and hemoglobin. Decreased plasma volume usually derives from several factors: increased sodium and chloride loss, decreased plasma bicarbonate, with altered carbon dioxide and oxygen tensions, albumin depletion, water and salt deprivation, severe fluid loss, with dehydration, and frank plasma loss. The first three factors primarily alter osmotic equilibria, they may be associated with abnormal

volume. A simple method of estimating blood volume from change in blood specific gravity following plasma infusion has been reported.⁹¹

It is to be hoped that consideration of the more fundamental concept of circulating proteins per unit of plasma volume will gradually supersede the often confusing two-dimensional measurement of plasma protein concentration. To this end, normal

TABLE 6 Conditions Associated with Alterations in Plasma Volume *

INCREASED PLASMA VOLUME		DECREASED PLASMA VOLUME	
I	Conditions associated with altered renal function or sodium retention or both Cardiac insufficiency, with congestive failure (II) ^{92, 93} associated with decreased cardiac output ⁹⁴ and increased venous pressure ^{92, 93, 95} Subacute or chronic glomerulonephritis when associated with edema, anemia and congestive failure (II) ⁹⁶ Excessive sodium intake (rare in normal persons) ⁹⁷ Steroid hormone ⁹⁸ and desoxycorticosterone administration ⁹⁹ Hypertonic glucose administration (transient)	I	Conditions associated with altered osmotic equilibria that may be associated with atered renal function a Increased sodium or chloride loss or both Chronic glomerulonephritis with hypoalbuminemia without edema ⁹⁶ Diarrhea especially in infants (II) Vomiting (II) ^{97, 100} Excessive sweating (II) ^{97, 100, 101} Addison's disease untreated (II) ^{102, 103} b Decreased plasma bicarbonate, altered carbon dioxide and oxygen tensions and decreased basal metabolic rate Pulmonary edema with infection ¹⁰⁰ Fulminant pneumonia (IV) ^{102, 101} Recovery phase of pneumonia ¹⁰¹ or congestive failure (Ia) ^{92, 93} (re active decrease) Starvation with ketosis (Ic) ^{97, 103} Diabetic acidosis (Ia) ¹¹⁰ Myxedema ¹¹² Acid salt diuresis (Ia) ^{97, 103} c Albumin depletion Malnutrition severe Cirrhosis with albumin depletion ⁹
II	Conditions associated with increased bicarbonate, altered carbon dioxide and oxygen tensions or increased basal metabolic rate Acute pneumococcal pneumonia ^{100, 101} Hyperthyroidism ¹⁰² Base administration ^{97, 100, 103}	II	Conditions associated with dehydration a Water deprivation and salt depletion ^{97, 103, 111, 112} b Severe fluid loss Diabetes insipidus ⁹⁷ Artificial fever (typhoid diathermy, infrared) (IIa) ¹¹³
III	Conditions associated with decreased circulating red-cell volume and hemoglobin (II) ¹⁰⁴ Secondary hypochromic anemia Hemolytic anemia Macrocytic anemia of unknown etiology Pernicious anemia ¹⁰⁵ Malaria without fever ¹⁰⁶	III	Conditions associated with plasma and blood loss (IV) a Acute hemorrhage ^{114, 115} Intestinal bleeding ¹¹⁵ Laceration of vessels ¹¹⁵ Skeletal trauma ¹¹⁵ b Local plasma loss ¹¹⁵ Burns Peritonitis
IV	Miscellaneous conditions Normal pregnancy (I) ¹⁰⁷ Lymphogranuloma inguinale ¹⁰⁴	IV	Conditions associated with peripheral vascular collapse Malaria at fastigium ¹⁰⁶

*Blood volume is altered in many conditions. In some cases a variation in the total red-cell volume is more significant than alteration of plasma volume as in chronic anemia and polycythemia. This table is confined to states in which plasma-volume changes have been observed and recently reported. Most frequently several conditions concurrently occur to modify plasma volume. The resultant of these influences determines the direction of plasma-volume change. The groupings as tabulated therefore are resultant expressions of various influences. Accordingly the various pathologic processes are somewhat inadequately tabulated under a single heading. When other associated conditions significantly modify the reported deviation they are indicated by the appropriate ipsilateral Roman numeral or letter or both, in parentheses.

renal function. Abnormal renal function may supervene, in association with peripheral vascular collapse.

Clinical measurements of the plasma volume are usually accomplished by injecting a given amount of an azo blue dye, T-1824, and determining the concentration (dilution) of dye in several plasma or serum samples obtained at stated intervals after injection. From these data, the plasma volume may be calculated.^{87, 88} A simplified technic, employing injection of a fixed amount of dye with subsequent withdrawal and analysis of a single blood sample at a given time thereafter, has been reported.^{89, 90} This modification provides a practicable clinical method for determining plasma

values and an incomplete tabulation of plasma volume and circulating plasma protein variations in disease are offered in Tables 5 and 6 — correlative to Tables 2 and 3, respectively.

(To be concluded)

REFERENCES

- Holman R. L., Mahoney E. B., and Whipple G. H. Blood plasma protein given by vein utilized in body metabolism. II. Dynamic equilibrium between plasma and tissue proteins. *J. Exper. Med.* 59: 269-282, 1934.
- Madden S. C. and Whipple G. H. Plasma proteins: their source, production and utilization. *Physiol. Rev.* 20: 194-217, 1940.
- Rose W. C. Nutritive significance of amino acids. *Physiol. Rev.* 18: 107-136, 1938.
- Rose, W. C. Role of protein in diet. *Proc. Inst. Med. Chicago* 15: 24, 1944.
- Schoenheimer R. *The Dynamic State of Body Constituents*. Harvard University Monographs in Medicine and Public Health No. 3, 78 pp. Cambridge, Massachusetts: Harvard University Press, 1941.

- 6 Schoenheimer, R, Ratner, S, Rittenberg, D, and Heidelberger, M. Interaction of blood proteins of rat with dietary nitrogen. *J Biol Chem* 144 541-544, 1942
- 7 Heidelberger, M, Trefera, H P, Schoenheimer, R, Ratner, S, and Rittenberg, D. Behavior of antibody protein toward dietary nitrogen in active and passive immunity. *J Biol Chem* 144 555-562, 1942
- 8 Tiselius, A. New apparatus for electrophoretic analysis of colloidal mixtures. *Tr Faraday Soc* 33 524 1937
- 9 Chemical, clinical, and immunological studies on products of human plasma fractionation. Chap II XIII. *J Clin Investigation* 23: 433-601, 1944
- 10 Cohn, E J. Chemical separation and clinical appraisal of components of blood. *Medicine* 24 333 1945
- 11 Cohn, E J, Strong, L F, Hughes, W L, Jr, Mulford, D J, Ashworth, J N, Melin, M, and Taylor, H L. Preparation and properties of serum and plasma proteins. IV. System for separation into fractions of protein and lipoprotein components of biological tissues and fluids. *J Am Chem Soc* 68 459-475, 1946
- 12 Cohn, E J, Oncley, J L, Strong, L E, Hughes, W L, Jr, and Armstrong, S H, Jr. Chemical, clinical, and immunological studies on products of human plasma fractionation. I. Characterization of protein fractions of human plasma. *J Clin Investigation* 23 417-432, 1944
- 13 Longworth, L G, Shedlovsky, T, and MacInnes, D A. Electrophoretic patterns of normal and pathological human blood serum and plasma. *J Exper Med* 70 339-413, 1939
- 14 Luetscher, J A, Jr. Electrophoretic analysis of plasma and urinary proteins. *J Clin Investigation* 19 313-320, 1940
- 15 Dole, V P. Electrophoretic patterns of normal plasma. *J Clin Investigation* 23 708-713, 1944
- 16 Moore, D H, and Lynn, J. Electrophoretic measurements on normal human plasma. *J Biol Chem* 141 819-825, 1941
- 17 Thorn, G W, Armstrong, S H, Jr, Davenport, V D, Woodruff, L M, and Tyler, E H. Chemical, clinical, and immunological studies on products of human plasma fractionation. XXX. Use of salt poor concentrated human serum albumin solution in treatment of chronic Bright's disease. *J Clin Investigation* 24 802-826, 1945
- 18 Trevor, V, Kaser, M, Patterson, J P, and Hill, R M. Plasma albumin globulin and fibrinogen in healthy individuals from birth to adulthood. II. Normal values. *J Lab & Clin Med* 27 471-486, 1941
- 19 Milam, D F. Plasma protein levels in normal individuals. *J Lab & Clin Med* 31 285-290, 1946
- 20 Cantarow, A, and Trumper, M. *Clinical Biochemistry*. Third edition. 647 pp. Philadelphia W B Saunders Company, 1945
- 21 Howe, P E. Use of sodium sulfate as globulin precipitant in determination of proteins in blood. *J Biol Chem* 49 93-107, 1921
- 22 Taylor, H L, and Keys, A. Fractionation of normal serum proteins by electrophoretic and sodium sulfate methods. *J Biol Chem* 148 379-381, 1943
- 23 Myers, V, and Muntwyler, E. Chemical changes in blood and their clinical significance. *Physiol Rev* 20 1-36, 1940
- 24 Rapoport, M, Rubin, M I, and Chaffee, D. Fractionation of serum and plasma proteins by salt precipitation in infants and children. I. Changes with maturity and age. II. Changes in glomerulonephritis. III. Changes in nephrosis. *J Clin Investigation* 22 487-497, 1943
- 25 Kagan, B M. Clinical significance of serum proteins. *South M J* 36 234-238, 1943
- 26 Phillips, R A, Van Slyke, D D, Dole, V P, Emerson, K., Jr, Hamilton, P B, and Archibald, R M. Copper sulfate method for measuring specific gravities of whole blood and plasma. Monograph Publications, Josiah Macy Jr Foundation 1945
- 27 Cohn, E J. Plasma proteins: their properties and functions. *Tr & Stud Coll Physicians Philadelphia* 10 149 162, 1942
- 28 Longworth, L G, Curtis, R M, and Pembroke, R H, Jr. Electrophoretic analysis of maternal and fetal plasmas and sera. *J Clin Investigation* 24 46-53, 1945
- 29 Brines, J K, Gibson, J G, 2d, and Kunkel, P. Blood volume in normal infants and children. *J Pediatr* 18 447-457, 1941
- 30 Gibson, J G, 2d, and Evans, W A, Jr. Clinical studies of blood volume. II. Relation of plasma and total blood volume to venous pressure, blood velocity rate, physical measurements, age, and sex pressure in ninety normal humans. *J Clin Investigation* 16 317-328, 1937
- 31 Stewart, J D, and Rourke, G M. On measurement of extracellular fluid volume with thiocyanate and body fluid analyses in 33 normal individuals. *J Lab & Clin Med* 26 1383-1387, 1941
- 32 Davis, L J. Determination of blood volume in man with Evans blue ("T 1824"). *Edinburgh M J* 49 465-483, 1942
- 33 Noble, R P, and Gregersten, M I. Blood volume in clinical shock. II. Extent and cause of blood volume reduction in traumatic, hemorrhagic and burn shock. *J Clin Investigation* 25 172-183, 1946
- 34 Weech, A A, Wollstein, M, and Goettsch, E. Nutritional edema in dog. V. Development of deficits in erythrocytes and hemoglobin on diet deficient in protein. *J Clin Investigation* 16 719-728, 1937
- 35 Moore, N S, and Van Slyke, D D. Relationships between plasma specific gravity, plasma protein content and edema in nephritis. *J Clin Investigation* 8 337-355, 1930
- 36 Keys, A, Taylor, H L, Mickelson, O., and Henschel, A. Famine edema and mechanism of its formation. *Science* 103 669, 1946
- 37 Davis, B D. Binding of sulfonamide drugs by plasma proteins. Factor in determining distribution of drugs in body. *J Clin Investigation* 22 753-762, 1943
- 38 Rawson, R A. Binding of T-1824 and structurally related diazo dyes by plasma proteins. *Am J Physiol* 138 708-717, 1943
- 39 Gray, S J. Mechanism of colloidal gold reaction of blood serum in liver disease. *Proc Soc Exper Biol & Med* 51 400 1942. Studies on mechanism of spinal fluid colloidal gold reaction. *Ibid* 51 401, 1942
- 40 Kabat, E A, Hanger, F M, Moore, D H, and Landow, H. Relation of cephalin flocculation and colloidal gold reactions to serum proteins. *J Clin Investigation* 22 563-568, 1943
- 41 Recant, L, Chergaff, E, and Hanger, F M. Comparison of cephalin-cholesterol flocculation with thymol turbidity test. *Proc Soc Exper Biol & Med* 60 245-247, 1945
- 42 Gray, S J, and Mitchell, E B. Effect of purified protein fractions on sedimentation rate of erythrocytes. *Proc Soc Exper Biol & Med* 51 403, 1942
- 43 Armstrong, S H, Jr. Personal communication
- 44 Janeway, C A, Gibson, S T, Woodruff, L M, Heyle, J T, Bailey, O T, and Newhouse, L R. Concentrated human serum albumin, albumin in treatment of shock, safety of albumin albumin in treatment of hypoproteinemia. *J Clin Investigation* 23 465-490, 1944
- 45 Cournaud, A, Noble, R P, Breed, E S, Lawson, H D, Baldwin, E DeF, Pinchot, G B, and Richards, D W, Jr. Clinical use of concentrated human serum albumin in shock, and comparison with whole blood and with rapid saline infusion. *J Clin Investigation* 23 491-505, 1944
- 46 Warren, J V, Stead, E A, Jr, Merrill, A J, and Brannon, E S. Treatment of shock with concentrated human serum albumin: preliminary report. *J Clin Investigation* 23 506-509, 1944
- 47 Heyl, J T, Gibson, J G, 2d, and Janeway, C A. Studies on plasma proteins. V. Effect of concentrated solutions of human and bovine serum albumin on blood volume after acute blood loss in man. *J Clin Investigation* 22 763-773, 1943
- 48 Metcalf, J. Unpublished data
- 49 Luetscher, J A, Jr. Effect of single injection of concentrated human serum albumin on circulating proteins and proteinuria in nephrosis. *J Clin Investigation* 23 365-371, 1944
- 50 Thorn, G W, Armstrong, S H, Jr, and Davenport, V D. Chemical, clinical, and immunological studies on products of human plasma fractionation. XXXI. Use of salt poor concentrated human serum albumin solution in treatment of hepatic cirrhosis. *J Clin Investigation* 25 304-323, 1946
- 51 Oncley, J L, Scatchard, G, and Brown, A. Physical chemical characteristics of certain proteins of normal human plasma. *J Physical Chem* (in press)
- 52 Gray, S J, and Barron, E S G. Electrophoretic analyses of serum proteins in diseases of liver. *J Clin Investigation* 22 191-200, 1943
- 53 Dole, V P, and Emerson, K, Jr. Electrophoretic changes in plasma protein patterns of patients with relapsing malaria. *J Clin Investigation* 24 644-647, 1945
- 54 Dole, V P, Watson, R F, and Rothbard, S. Electrophoretic changes in serum protein patterns of patients with scarlet fever and rheumatic fever. *J Clin Investigation* 24 648-656, 1945
- 55 Malmros, H, and Blix, G. Plasma proteins in cases with high sedimentation rates. *Acta Med Scandinavica* Suppl 170 280-306, 1946
- 56 Chow, B F. Electrophoretic studies on effect of protein depletion on plasma proteins and regeneration of plasma proteins after oral administration of hydrolysates prepared from casein and lactalbumin. New York Acad of Sc Conference on Protein Hydrolysis, December 1945
- 57 Bjorndal, M. Serum proteins during immunization. *Acta path. & microbiol Scandinavica* 20 221 1943
- 58 Longworth, L G, and MacInnes, D A. Electrophoretic study of nephrotic sera and urine. *J Exper Med* 71 77-82, 1940
- 59 Moore, D H, Kabat, E A, and Gutman, A B. Bence-Jones proteinemia in multiple myeloma. *J Clin Investigation* 22 67-75, 1943
- 60 Blackman, S S, Jr, Barker, W H, Buell, M V, and Davis, B D. On pathogenesis of renal failure associated with multiple myeloma. Electrophoretic and chemical analysis of protein in urine and blood serum. *J Clin Investigation* 23 163-166, 1944
- 61 Lewis, L A, Schneider, R W, and McCullagh, E P. Tiselius electrophoresis studies of plasma proteins in diabetes mellitus. *J Clin Endocrinol* 4 535-539, 1944
- 62 Pillemer, L, Oncley, J L, Melin, M, Elliott, J, and Hutchings, M C. Separation and concentration of isohemagglutinins from group-specific human plasma. *J Clin Investigation* 23 550-553, 1944
- 63 DeGowin, E L. Appraisal of isohemagglutinin activity. *J Clin Investigation* 23 554-556, 1944
- 64 Ende, F C. Concentrations of certain antibodies in globulin fractions derived from human blood plasma. *J Clin Investigation* 23 510-530, 1944
- 65 Kabat, E A. Immunochemistry of proteins. *J Immunol* 47:511-587, 1943
- 66 Dougherty, T F, Chase, J H, and White, A. Demonstration of antibodies in lymphocytes. *Proc Soc Exper Biol & Med* 57 295-298, 1944
- 67 Kass, E H. Occurrence of normal serum gamma globulin in human lymphocytes. *Science* 101 337, 1945
- 68 Dougherty, T F, Chase, J H, and White, A. Pituitary adrenal cortical control of antibody release from lymphocytes. Explanation of amnesic response. *Proc Soc Exper Biol & Med* 58 135-140, 1945
- 69 Coburn, A F, and Moore, D H. Plasma proteins in disseminated lupus erythematosus. *Bull Johns Hopkins Hosp* 73 196-221, 1943
- 70 Davis, B D, Moore, D H, Kabat, E A, and Harris, A. Electrophoretic, ultracentrifugal and immunochemical studies on Wassermann antibody. *J Immunol* 50 1-20, 1945
- 71 Krebs, E G. Depression of gamma globulin in hypoproteinemia due to malnutrition. *J Lab & Clin Med* 31 85-89, 1946
- 72 Cannon, R, Chase, W E, and Wiessler, R W. Relationship of protein reserves to antibody production. I. Effects of low protein diet and of plasmapheresis upon formation of agglutinins. *J Immunol* 47 133-147, 1943
- 73 Stokes, J R, Maris, E P, and Gellis, S S. Use of concentrated normal human serum gamma globulin (human immune serum globulin) in prophylaxis and treatment of measles. *J Clin Investigation* 23 531-540, 1944
- 74 Ordman, C W, Jennings, C G, and Janeway, C A. Use of concentrated normal human serum gamma globulin (human immune serum globulin) in prevention and attenuation of measles. *J Clin Investigation* 23 541-549, 1944
- 75 Gellis, S S, Stokes, J R, Brother, G M, Hall, W M, Gilmore, H R, Beyer, E, and Morniey, R A. Use of human immune serum globulin (gamma globulin) in infectious (epidemic) hepatitis in Mediterranean theater of operations. I. Studies on prophylaxis in two epidemics of infectious hepatitis. *J A M A* 128 1062, 1945
- 76 Havens, W F, Jr., and Paul, J R. Prevention of infectious hepatitis with gamma globulin. *J A M A* 129 270-272, 1945
- 77 Gellis, S S, McGuinness, A C, and Peters, M. Study on prevention of mumps orchitis by gamma globulin. *Am J M Sc* 210 661-664, 1945

- 78 Ham, T H., and Curtiss F C Plasma fibrinogen response in man influence of nutritional state, induced hyperpyrexia infectious disease and liver damage *Medicine* 17 413-445 1938
- 79 Morrison, I R Qualitative changes in fibrinogen which influence erythrocyte sedimentation rate and clot retraction time *Am J Med Sci* 211:325-331, 1946
- 80 Peters J P Serum proteins in health and disease *J Mt Sinai Hosp* 9 127-141, 1942
- 81 Sabin F R Cellular reactions to dye-protein with concept of the mechanism of antibody formation *J Exper Med* 70:67-82 1939
- 82 Brand E Kassel B and Saidel L J Amino acid and composition of plasma proteins *J Clin Investigation* 23 437-444, 1944
- 83 Bruckman, F S, D Esopo L M., and Peters, J P Plasma proteins in relation to blood hydration IV. Malnutrition and serum proteins *J Clin Investigation* 8 577-590 1950
- 84 Hopper J., Jr., Winkler A W and Elkington J R. Simultaneous measurements of blood volume in man and dog by means of Evans blue dye T-1824 and by means of carbon monoxide II Under abnormal conditions including secondary shock *J Clin Investigation* 23 636-648 1944
- 85 Metcoff J Favour C B, and Stare F J Plasma protein and hemoglobin in protein-deficient rat three-dimensional study *J Clin Investigation* 24 82-91 1945
- 86 Lyons, R. C., Jacobson S D and Neerkin J L. Relationship between changes in serum protein concentration and plasma volume in normal subjects *J Lab & Clin Med* 30 404-411 1945
- 87 Gregersen, M I, Gibson J G 2d and Stead E A. Plasma volume determination with dyes errors in colorimetry: use of blue dye T-1824 *Am J Physiol* 113:34 1935
- 88 Gibson J G 2d and Evans W A., Jr. Clinical studies of blood volume I Clinical application of method employing azo dye "Evans blue" and spectrophotometer *J Clin Investigation* 16 301-316, 1937
- 89 Gregersen M I Practical method for determination of blood volume with dye T-1824 survey of present basis of dye method and its clinical applications *J Lab & Clin Med* 29 1266-1286 1944
- 90 Noble R P and Gregersen, M I Blood volume in clinical shock I Mixing time and disappearance rate of T 1824 in normal subjects and in patients in shock determination of plasma volume in man from 10-minute sample *J Clin Investigation* 25 158-171 1946
- 91 Phillips R A., Yeomans A., Dole V P, Farr, L. E., and Van Slyke D D Estimation of blood volume from change in blood specific gravity following plasma infusion *J Clin Investigation* 25 261-269, 1946
- 92 Gibson, J G. 2d and Evans W A., Jr. Clinical studies of blood volume III Changes in blood volume venous pressure and blood velocity rate in chronic congestive heart failure. *J Clin Investigation* 16 851-858 1937
- 93 Meneely G R. and Kaltreider N L. Study of volume of blood in congestive heart failure Relation to other measurements in 15 patients *J Clin Investigation* 22:521-530 1943
- 94 Merrill A J Edema and decreased renal blood flow in patients with chronic congestive heart failure evidence of "forward failure" as primary cause of edema *J Clin Investigation* 25:389-400 1946
- 95 Perera G A Increased plasma volume in cardiac insufficiency its correlation with right-sided failure *J Clin Investigation* 24 708-711 1945
- 96 Harris A W and Gibson J G 2d Clinical studies of blood volume VII Changes in blood volume in Bright's disease with or without edema renal insufficiency or congestive heart failure and in hypertension *J Clin Investigation* 28:527-536, 1939
- 97 Peters J P. Water exchange *Physiol Rev* 24:491-531 1944
- 98 Thorn G W., Nelson K R., and Thorn D W. Study of mechanism of edema associated with menstruation *Endocrinology* 22 155-163 1938
- 99 Clinton M., Jr., and Thorn G W Effect of desoxycorticosterone acetate administration on plasma volume and electrolyte balance of normal human subjects *Bull Johns Hopkins Hosp* 72 255-264 1943
- 100 Soule H. C. Buckman, T E and Darrow D C. Blood volume in fever *J Clin Investigation* 5 229-242 1928
- 101 Rutstein D D., Thompson, K. J., Tolmach D M Walter W W and Floody R. J Plasma volume and "extravascular thiocyanate space" in pneumococcus pneumonia *J Clin. Investigation* 24 11-20 1945
- 102 Gibson, J G. 2d and Harris A W Clinical studies of blood volume V. Hyperthyroidism and myxedema *J Clin Investigation* 18 59-65, 1939
- 103 Peters J P., and Van Slyke, D D *Quantitative Clinical Chemistry - Volume I* 1264 pp Baltimore Williams & Wilkins Company 1951
- 104 Gibson, J G., 2d Harris A W and Swigert V W Clinical studies of blood volume VIII Macrocytic and hypochromic anemias due to chronic blood loss hemolysis and miscellaneous causes and polycythemia vera *J Clin Investigation* 18 621-632 1939
- 105 Gibson J G., 2d Clinical studies of blood volume VI Changes in blood volume in pernicious anemia in relation to hematopoietic response to intramuscular liver extract therapy *J Clin Investigation* 18 401-414 1939
- 106 Feldman H A., and Murphy F D Effect of alterations in blood volume on anemia and hypoproteinemia of human malaria *J Clin Investigation* 24 780-792 1945
- 107 Thomson, K J., Hirsheimer, A Gibson J G., II and Evans W A., Jr. Studies on circulation in pregnancy III Blood volume changes in normal pregnant women *Am J Obst & Gynec* 36 48-59 1938
- 108 Swingle W W Parkins W M., Taylor A R. and Hays, H W Study of water intoxication in intact and adrenalectomized dog and influence of adrenal cortical hormone upon fluid and electrolyte distribution *Am J Physiol* 119:557-566 1937
- 109 Thorn G W., Howard, R. R. and Emerson K., Jr. Treatment of Addison's disease with desoxy-corticosterone acetate synthetic adrenal cortical hormone (preliminary report) *J Clin Investigation* 18 449-467 1939
- 110 Jacobson S D and Lyons R H Changes in blood volume produced by diabetic acidosis *J Lab & Clin Med* 27 1169-1173 1942
- 111 Darrow D C and Yannet, H Metabolic studies of changes in body electrolyte and distribution of body water induced experimentally by deficit of extracellular electrolyte *J Clin Investigation* 15:419-427, 1936
- 112 Winkler A W., Danowski T S., Elkington J R. and Peters J P. Electrolyte and fluid studies during water deprivation and starvation in human subjects and effect of ingestion of fish of carbohydrate and of salt solutions *J Clin. Investigation* 23 807-815 1944
- 113 Gibson J G 2d and Kopp I. Studies in physiology of artificial fever I Changes in blood volume and water balance *J Clin Investigation* 17 219-232 1938
- 114 Ebert, R. V Stead E A Jr. and Gibson J G II Response of normal subjects to acute blood loss with special reference to mechanism of restoration of blood volume *Arch Int Med* 68 578-590 1941
- 115 Richards D W. Jr. Circulation in traumatic shock in man Harvey Lecture *Bull New York Acad Med* 20:363-393 1944

- 6 Schoenheimer, R., Ratner, S., Rittenberg, D., and Heidelberger, M. Interaction of blood proteins of rat with dietary nitrogen. *J Biol Chem* 144 541-544, 1942
- 7 Heidelberger, M., Trefers, H. P., Schoenheimer, R., Ratner, S., and Rittenberg, D. Behavior of antibody protein toward dietary nitrogen in active and passive immunity. *J Biol Chem* 144 555-562, 1942
- 8 Tiselius, A. New apparatus for electrophoretic analysis of colloidal mixtures. *Tr Faraday Soc* 33 524, 1937
- 9 Chemical, clinical, and immunological studies on products of human plasma fractionation. Chap II-XIII. *J Clin Investigation* 23 433-601, 1944
- 10 Cohn, E. J. Chemical separation and clinical appraisal of components of blood. *Medicine* 24 333-338, 1945
- 11 Cohn, E. J., Strong, L. E., Hughes, W. L., Jr., Mulford, D. J., Ashworth, J. N., Melin, M., and Taylor, H. L. Preparation and properties of serum and plasma proteins. IV. System for separation into fractions of protein and lipoprotein components of biological tissues and fluids. *J Am Chem Soc* 68 459-475, 1946
- 12 Cohn, E. J., Oncley, J. L., Strong, L. E., Hughes, W. L., Jr., and Armstrong, S. H., Jr. Chemical, clinical, and immunological studies on products of human plasma fractionation. I. Characterization of protein fractions of human plasma. *J Clin Investigation* 23 417-432, 1944
- 13 Longworth, L. G., Shedlovsky, T., and MacInnes, D. A. Electrophoretic patterns of normal and pathological human blood serum and plasma. *J Exper Med* 70 339-413, 1939
- 14 Luetscher, J. A. Jr. Electrophoretic analysis of plasma and urinary proteins. *J Clin Investigation* 19 313-320, 1940
- 15 Dole, V. P. Electrophoretic patterns of normal plasma. *J Clin Investigation* 23 708-713, 1944
- 16 Moore, D. H., and Linn, J. Electrophoretic measurements on normal human plasma. *J Biol Chem* 141 819-825, 1941
- 17 Thorn, G. W., Armstrong, S. H., Jr., Davenport, V. D., Woodruff, L. M., and Tyler, F. H. Chemical, clinical, and immunological studies on products of human plasma fractionation. XXX. Use of salt poor concentrated human serum albumin solution in treatment of chronic Bright's disease. *J Clin Investigation* 24 802-828, 1945
- 18 Trevorrow, V., Kaser, M., Patterson, J. P., and Hill, R. M. Plasma albumin globulin and fibrinogen in healthy individuals from birth to adulthood. II. Normal values. *J Lab & Clin Med* 27 471-486, 1941
- 19 Milam, D. F. Plasma protein levels in normal individuals. *J Lab & Clin Med* 31 285-290, 1946
- 20 Cantarow, A., and Trumper, M. *Clinical Biochemistry*. Third edition. 647 pp. Philadelphia, W. B. Saunders Company, 1945
- 21 Howe, P. E. Use of sodium sulfate as globulin precipitant in determination of proteins in blood. *J Biol Chem* 49 93-107, 1921
- 22 Taylor, H. L., and Keys, A. Fractionation of normal serum proteins by electrophoretic and sodium sulfate methods. *J Biol Chem* 148 379-381, 1943
- 23 Myers, V. C., and Muntwyler, E. Chemical changes in blood and their clinical significance. *Physiol Rev* 20 1-36, 1940
- 24 Rapoport, M., Rubin, M. I., and Chaffee, D. Fractionation of serum and plasma proteins by salt precipitation in infants and children. I. Changes with maturity and age. II. Changes in glomerulonephritis. III. Changes in nephrosis. *J Clin Investigation* 22 487-497, 1943
- 25 Kagan, B. M. Clinical significance of serum proteins. *South M J* 36 234-238, 1943
- 26 Phillips, R. A., Van Slyke, D. D., Dole, V. P., Emerson, K., Jr., Hamilton, P. B., and Archibald, R. M. Copper sulfate method for measuring specific gravities of whole blood and plasma. Monograph Publications. Josiah Macy, Jr. Foundation, 1945
- 27 Cohn, E. J. Plasma proteins their properties and functions. *Tr & Stud, Coll Physicians Philadelphia* 10 149-162, 1942
- 28 Longworth, L. G., Curtis, R. M., and Pembroke, R. H., Jr. Electrophoretic analysis of maternal and fetal plasmas and sera. *J Clin Investigation* 24 46-53, 1945
- 29 Brines, J. K., Gibson, J. G. 2d, and Kunkel, P. Blood volume in normal infants and children. *Pediatr* 18 447-457, 1941
- 30 Gibson, J. G. 2d, and Evans, W. A., Jr. Clinical studies of blood volume. II. Relation of plasma and total blood volume to venous pressure, blood velocity rate, physical measurements, age and sex, in ninety normal humans. *J Clin Investigation* 16 317-328, 1937
- 31 Stewart, J. D., and Rourke, G. M. On measurement of extracellular fluid volume with thiocyanate and body fluid analysis in 33 normal individuals. *J Lab & Clin Med* 26 1383-1387, 1941
- 32 Davis, L. J. Determination of blood volume in man with Evans blue ("T-1824"). *Edinburgh M J* 49 465-483, 1942
- 33 Noble, R. P., and Gregersen, M. I. Blood volume in clinical shock. II. Extent and cause of blood volume reduction in traumatic, hemorrhagic and burn shock. *J Clin Investigation* 25 172-183, 1946
- 34 Weech, A. A., Wollstein, M., and Goettsch, E. Nutritional edema in dog. V. Development of deficits in erythrocytes and hemoglobin on diet deficient in protein. *J Clin Investigation* 16 719-728, 1937
- 35 Moore, N. S., and Van Slyke, D. D. Relationships between plasma specific gravity, plasma protein content and edema in nephritis. *J Clin Investigation* 8 337-355, 1930
- 36 Keys, A., Taylor, H. L., Mickelson, O., and Henschel, A. Famine edema and mechanism of its formation. *Science* 103 669, 1946
- 37 Davis, B. D. Binding of sulfonamide drugs by plasma proteins. Factor in determining distribution of drugs in body. *J Clin Investigation* 22 753-762, 1943
- 38 Rawson, R. A. Binding of T-1824 and structurally related diazo dyes by plasma proteins. *Am J Physiol* 138 708-717, 1943
- 39 Gray, S. J. Mechanism of colloidal gold reaction of blood serum in liver disease. *Proc Soc Exper Biol & Med* 51 400, 1942. Studies on mechanism of spinal fluid colloidal gold reaction. *Ibid* 51 401, 1942
- 40 Kabat, E. A., Hanger, F. M., Moore, D. H., and Landow, H. Relation of cephalin flocculation and colloidal gold reactions to serum proteins. *J Clin Investigation* 22 563-568, 1943
- 41 Recant, L., Chagraff, E., and Hanger, F. M. Comparison of cephalin-cholesterol flocculation with thymol turbidity test. *Proc Soc Exper Biol & Med* 60 245-247, 1945
- 42 Gray, S. J., and Mitchell, E. B. Effect of purified protein fractions on sedimentation rate of erythrocytes. *Proc Soc Exper Biol & Med* 51 403, 1942
- 43 Armstrong, S. H., Jr. Personal communication
- 44 Janeway, C. A., Gibson, S. T., Woodruff, L. M., Heyle, J. T., Bailey, O. T., and Newhouser, L. R. Concentrated human serum albumin albumin in treatment of shock: safety of albumin albumin in treatment of hypoproteinemia. *J Clin Investigation* 23 465-490, 1944
- 45 Cournaud, A., Noble, R. P., Breed, E. S., Lawson, H. D., Baldwin, E. DeF., Pinchot, G. B., and Richards, D. W., Jr. Clinical use of concentrated human serum albumin in shock, and comparison with whole blood and with rapid saline infusion. *J Clin Investigation* 23 491-505, 1944
- 46 Warren, J. V., Stead, E. A., Jr., Merrill, A. J., and Brannon, E. E. Treatment of shock with concentrated human serum albumin: preliminary report. *J Clin Investigation* 23 506-509, 1944
- 47 Heyl, J. T., Gibson, J. G. 2d, and Janeway, C. A. Studies on plasma proteins. V. Effect of concentrated solutions of human and bovine serum albumin on blood volume after acute blood loss in man. *J Clin Investigation* 22 763-773, 1943
- 48 Metcalf, J. Unpublished data
- 49 Luetscher, J. A., Jr. Effect of single injection of concentrated human serum albumin on circulating proteins and proteinuria in nephrosis. *J Clin Investigation* 23 365-371, 1944
- 50 Thorn, G. W., Armstrong, S. H., Jr., and Davenport, V. D. Chemical clinical and immunological studies on products of human plasma fractionation. XXXI. Use of salt-poor concentrated human serum albumin solution in treatment of hepatic cirrhosis. *J Clin Investigation* 25 304-323, 1946
- 51 Oncley, J. L., Scatchard, G., and Brown, A. Physical chemical characteristics of certain of proteins of normal human plasma. *J Physical Chem* (in press)
- 52 Gray, S. J., and Barron, E. S. G. Electrophoretic analyses of serum proteins in diseases of liver. *J Clin Investigation* 22 191-200, 1943
- 53 Dole, V. P., and Emerson, K. Jr. Electrophoretic changes in plasma protein patterns of patients with relapsing malaria. *J Clin Investigation* 24 644-647, 1945
- 54 Dole, V. P., Watson, R. F., and Rothbard, S. Electrophoretic changes in serum protein patterns of patients with scarlet fever and rheumatic fever. *J Clin Investigation* 24 648-656, 1945
- 55 Malmros, H., and Blix, G. Plasma proteins in cases with high sedimentation rates. *Acta Med Scandinav Suppl* 170 280-306, 1946
- 56 Chow, B. F. Electrophoretic studies on effect of protein depletion on plasma proteins and regeneration of plasma proteins after oral administration of hydrolyzates prepared from casein and lactalbumin. New York Acad. of Sc. Conference on Protein Hydrolyzates, December, 1945
- 57 Bjorneboe, M. Serum proteins during immunization. *Acta path & microbiol Scandinav* 20 221, 1943
- 58 Longworth, L. G., and MacInnes, D. A. Electrophoretic study of nephrotic sera and urine. *J Exper Med* 71 77-82, 1940
- 59 Moore, D. H., Kabat, E. A., and Gutman, A. B. Bence-Jones proteinemia in multiple myeloma. *J Clin Investigation* 22 67-75, 1943
- 60 Blackman, S. S., Jr., Barker, W. H., Buell, M. V., and Davis, B. D. On pathogenesis of renal failure associated with multiple myeloma. Electrophoretic and chemical analysis of protein in urine and blood serum. *J Clin Investigation* 23 163-166, 1944
- 61 Lewis, L. A., Schneider, R. W., and McCullagh, E. P. Tiselius electrophoresis studies of plasma proteins in diabetes mellitus. *J Clin Endocrinol* 4 535-539, 1944
- 62 Pillemer, L., Oncley, J. L., Melin, M., Elliott, J., and Hutchinson, M. C. Separation and concentration of isohemagglutinins from group-specific human plasma. *J Clin Investigation* 23 550-553, 1944
- 63 DeGowin, E. L. Appraisal of isohemagglutinin activity. *J Clin Investigation* 23 554-556, 1944
- 64 Enders, J. F. Concentrations of certain antibodies in globulin fractions derived from human blood plasma. *J Clin Investigation* 23: 510-530, 1944
- 65 Kabat, E. A. Immunochemistry of proteins. *J Immunol* 47 513-587, 1943
- 66 Dougherty, T. F., Chase, J. H., and White, A. Demonstration of antibodies in lymphocytes. *Proc Soc Exper Biol & Med* 57 295-298, 1944
- 67 Kass, E. H. Occurrence of normal serum gamma globulin in human lymphocytes. *Science* 101 337, 1945
- 68 Dougherty, T. F., Chase, J. H., and White, A. Pituitary adrenal cortical control of antibody release from lymphocytes. Explanation of anamnestic response. *Proc Soc Exper Biol & Med* 58 135-140, 1945
- 69 Coburn, A. F., and Moore, D. H. Plasma proteins in disseminated lupus erythematosus. *Bull Johns Hopkins Hosp* 73 196-221, 1943
- 70 Davis, B. D., Moore, D. H., Kabat, E. A., and Harris, A. Electrophoretic, ultracentrifugal, and immunochemical studies on Wassermann antibody. *J Immunol* 50 1-20, 1945
- 71 Krebs, B. G. Depression of gamma globulin in hypoproteinemia due to malnutrition. *J Lab & Clin Med* 31 85-89, 1946
- 72 Cannon, P. R., Chase, W. E., and Wislar, R. W. Relationship of protein reserves to antibody production. I. Effects of low-protein diet and of plasmapheresis upon formation of agglutinins. *J Immunol* 47 133-147, 1943
- 73 Stokes, J. R., Marns, E. P., and Gellis, S. S. Use of concentrated normal human serum gamma globulin (human immune serum globulin) in prophylaxis and treatment of measles. *J Clin Investigation* 23 531-540, 1944
- 74 Ordman, C. W., Jennings, C. G., and Janeway, C. A. Use of concentrated normal human serum gamma globulin (human immune serum globulin) in prevention and attenuation of measles. *J Clin Investigation* 23 541-549, 1944
- 75 Gellis, S. S., Stokes, J. R., Brothier, G. M., Hall, W. M., Gilmore, H. R., Beyer, E., and Moroney, R. A. Use of human immune serum globulin (gamma globulin) in infectious (epidemic) hepatitis in Mediterranean Theater of Operations. I. Studies on prophylaxis in two epidemics of infectious hepatitis. *J A M A* 128 1062-1065, 1945
- 76 Evans, W. P., Jr., and Paul, J. R. Prevention of infectious hepatitis with gamma globulin. *J A M A* 129 270-272, 1945
- 77 Gellis, S. S., McGuinness, A. C., and Peters, M. Study on prevention of mumps orchitis by gamma globulin. *Am J M Sc* 210 661-664, 1945

We are constantly reminded that the patient was associated with animals, both sick and well. This suggests tularemia and brucellosis, which in this vicinity are more chronic in their course, without pronounced affection of the nervous system. Rabies runs a course even shorter than that in this case. The chief symptom — hydrophobia — is not mentioned, and the spinal fluid in such cases is normal. As for distemper, it is my understanding that this disease does not attack man.

Food poisoning, suggested by the fact that the patient and his family had mild attacks of diarrhea, indicates the possibility of botulism and other neurotropic poisons. It is my impression that none of these give abnormal spinal-fluid findings, nor is the gastrointestinal picture a dominant one. Myasthenia gravis may cause death from respiratory paralysis as may infectious poliomyelitis. But the clinical picture and course are so different from those in the case under discussion that they can hardly be considered.

A frequent cause of acute bulbar palsy is thrombosis of the basilar artery or its branches. In a patient of this age the usual etiologic factor, arteriosclerosis, should be absent. The presence of a septic embolus may be considered because of the cardiac murmur, but it is usual for emboli to pass up the internal carotid arteries rather than the vertebral vessels.

By process of exclusion, none of the above diagnoses fit this case. The onset, the clinical course, the symptomatology and the physical and spinal-fluid findings are typical of acute poliomyelitis of the bulbar type, which is my diagnosis. Incidentally, if this case had been reported twenty-five years ago, I should have included encephalitis lethargica as of equal likelihood to poliomyelitis — the findings in the bulbar types of that disease were in every way consistent with those in this patient. My diagnosis of acute poliomyelitis of the bulbar type is made with the reservation that my knowledge of animal diseases causing virus infections of the nervous system is limited.

DR AUGUSTUS S. ROSE: I should like to ask Dr Ayer to discuss the recurrence of the Babinski sign.

DR AYER: It sometimes happens in poliomyelitis that, although the gray matter is primarily involved, the white matter is also infiltrated and a transitory, not a permanent, Babinski sign is found. That was characteristic of the cases of encephalitis lethargica that simulated poliomyelitis. Also, one wonders if the Babinski sign was persistent, a single observation of a positive sign must be confirmed.

DR ROSE: I should also like to ask about the absence of a stiff neck in bulbar poliomyelitis.

DR AYER: That is not so frequent in this type as in poliomyelitis affecting the spinal cord.

There are two additional points that should be mentioned. In an epidemic in this vicinity some

years ago, Crone* analyzed a series of cases of bulbar poliomyelitis in which the reaction of the patients in the respirator was of great interest. They died not only in spite of the respirator but also, perhaps, because of it. It is interesting that in this case the intercostal muscles were spared.

The second point is that in these cases the higher the sugar in the spinal fluid, the worse the prognosis, that has never been explained to my knowledge. The sugar was elevated in this case. The temperature was high for the usual case of poliomyelitis. Why did you not ask about that? Patients with bulbar poliomyelitis often run high temperatures, whereas those with the ordinary type run temperatures of around 100 to 102°F — usually 101°F.

DR CHARLES S. KUBIK: You saw the patient Dr. Rose. Do you wish to add anything?

DR ROSE: We thought that this was a case of bulbar poliomyelitis. We considered the extensor plantar reflex on the one hand and the difficulty in the respirator on the other to have been due to bulbar involvement outside the anterior-horn cells — in other words, that encephalitis, as well as anterior poliomyelitis, was present.

DR AYER: The diagnosis may well include encephalitis, but the terminal picture was hardly enough to indicate encephalitis because anoxemia offers a sufficient explanation.

CLINICAL DIAGNOSIS

Anterior poliomyelitis, bulbar type

DR AYER'S DIAGNOSIS

Acute poliomyelitis, bulbar type

ANATOMICAL DIAGNOSIS

Poliomyelitis, bulbar type

PATHOLOGICAL DISCUSSION

DR KUBIK: This was a case of poliomyelitis. The temperature, which was high on admission, dropped and rose again. Because of the difficulty in swallowing, the question of aspiration pneumonia was raised. There was bronchopneumonia, but no definite aspiration pneumonia. As in most fatal cases of poliomyelitis there were lesions not only in the medulla and spinal cord but also in the pons, midbrain, basal ganglions and cerebral cortex.

The cortical lesions are usually not extensive, and so far as I know never give rise to focal signs, in my experience they are likely to be found in the anterior central convolutions. Another interesting feature is that there is usually good functional recovery of the paralyzed bulbar muscles in nonfatal cases of poliomyelitis and that there is, as a rule, comparatively little destruction of the nerve cells.

*Crone, A. L. Treatment of acute poliomyelitis with respirator. *New Eng. J. Med.* 210: 621-623, 1934.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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CASE 33011

PRESENTATION OF CASE

A thirty-five-year-old operator of a mink farm and dog kennel entered the hospital because of difficulty in swallowing.

Eight days before entry the patient, as well as the other members of his family, had had a mild bout of diarrhea, which had subsided completely in two days. Four days before entry he noticed a slight pain in the back and on the next day developed nausea and vomiting. In the evening the temperature rose to 100.5°F. Vomiting continued, the palate became sore and swollen, and the temperature rose to 102°F. On the day of admission the nausea abated, but difficulty in swallowing developed, so that mucus and saliva collected in the throat, causing great discomfort and difficulty in breathing. The patient gagged on liquids unless he was extremely careful. He regurgitated fluids through his nose and could not open his mouth as wide as usual. He had had no headaches, diplopia, pain, muscle tenderness or cough.

During the previous winter many of the patient's dogs had died from a virus infection identified at a state university as similar to but not identical with distemper.

Physical examination revealed a well nourished man whose respirations were shallow but not rapid. He was not cyanotic. The voice was thick and indistinct and had a nasal quality. The pharynx was injected. There was a Grade II, blowing systolic murmur heard best over the sternum slightly to the left of the midline in the third interspace. The lungs and abdomen were normal. Neurologic examination showed a questionable weakness of the left side of the face. The pharyngeal constrictors were weak. The neck muscles—particularly the right sternomastoid—were weak. The neck was not stiff. The arms and legs had good strength. There was no muscle tenderness. The tendon reflexes in the arms were not obtainable. The right knee jerk was questionably absent, the left knee jerk and both ankle jerks were present. There was an extensor plantar reflex on the right. Sensation was normal.

The temperature was 104.3°F, the pulse 80 and the respirations 28. The blood pressure was 140 systolic, 60 diastolic.

Examination of the blood disclosed a hemoglobin of 16 gm and a white-cell count of 12,000, with 72 per cent neutrophils. The urine was normal. The spinal fluid had an initial pressure equivalent to 200 mm of water. There were 26 lymphocytes and 2 polymorphonuclear leukocytes per cubic millimeter. The total protein was 70 mg, the sugar 86 mg and the chloride 667 mg per 100 cc. The gold-sol test was 0001232110.

Despite frequent suctioning of the pharynx the patient was unable to sleep because of the accumulating mucus. The respirations were good. On the second hospital day, the temperature dropped to 100°F, and he appeared somewhat improved. Nevertheless he was started on prophylactic penicillin at the rate of 24,000 units every three hours. During the night, he again had difficulty with mucus. On the third hospital day he was disoriented and picking at the bedclothes. Breathing was good, and the chest clear. The temperature rose to 101°F.

On the fourth hospital day the patient was unresponsive, cyanotic and bathed in perspiration. The lungs were clear, and the chest expanded well without the use of accessory muscles. The temperature now fell to 98°F. After the administration of oxygen by mask the cyanosis diminished and the pulse rate improved. The patient was then placed in a respirator. Breathing was gasping, irregular and asynchronous with the respirator. Mucus gathered rapidly. The pulse gradually became too weak to be felt. Finally, respirations ceased.

DIFFERENTIAL DIAGNOSIS

DR JAMES B AYER. We are evidently dealing with a rapidly progressive, acute, febrile disturbance affecting chiefly the brain stem, particularly the medulla. That a lesion or lesions were present in the medulla is indicated by the abnormal findings in the spinal fluid, which suggest either a virus infection or a reaction to local irritation. Although the lesion was dominant in the medulla and pons and undoubtedly caused the patient's death, there is some evidence that the spinal cord was also involved, as shown by the absent reflexes in the arms and the unequal reflexes in the legs. The terminal disorientation does not necessarily indicate implication of the cortex, the mental picture being readily explained on the basis of anoxemia.

In so-called "acute bulbar palsy" many diagnoses must be considered. All forms of acute bacterial meningitis are excluded by the absence of meningeal symptoms and by the type of spinal fluid.

Diphtheria is a possibility, but the lack of mention of a membrane in the throat and the abnormal spinal-fluid findings exclude this diagnosis.

time I do not know what the red macules on the chest were. They may have been important.

DR TRACY B. MALLORY: The dermatologist's opinion was that they were characteristic of bromide rash.

DR AUB: The scoliosis immediately makes one doubt the significance of any physical findings in the chest, because as soon as severe scoliosis is encountered, physical findings in the chest are altered by changes in aeration in the lung. The increased white-cell count and the red cells in the urine could have been due to hypernephroma involving the vena cava and obstructing the return blood flow from the other kidney, or to metastases to the other kidney.

The course suggests metastases not from the lung but from elsewhere, and one thinks, of course, of hypernephroma. The elevated temperature might have been due to either a primary infection or one caused by an occluding neoplasm. It does not establish an infection, however, because hypernephroma in itself causes fever. The pleuritic pain is also somewhat more suggestive of hypernephroma than of primary tumor of the lung, unless there was a good deal of infection, with subsequent irritation of the pleura, due to the primary tumor of the lung.

The patient was operated on on the eighth day. The type of procedure performed must be questioned. This was not the type of case that requires an extensive operation. If this man had been my patient, I should have handled him by doing a bronchoscopy, which is probably the operation that is referred to.

In these discussions I do not like to put in every possible diagnosis so as to be sure to include everything that was wrong with the patient. I think that it is better to list only likely diagnoses. There are three probable diagnoses in this case. One is primary infection of the lung that lasted four months and came and went, giving the recurrent symptoms, but that seems unlikely. Although the first bronchoscopy showed only chronic infection, a primary bronchiogenic neoplasm and metastases of a hypernephroma are the other two conditions that need serious thought. The diagnosis practically depends on the x-ray films. I do not believe that a proper differential diagnosis can be made without inspection of the films, but before that I should like to make one or two remarks. I think that this was probably a neoplasm, the most important thing is the location. If it was close to the hilar region, one must make the diagnosis of a primary, bronchiogenic neoplasm, with infection behind it caused by obstruction of the bronchus. If the neoplasm was out in the periphery it was probably metastatic hypernephroma. A duration of six years is not too long for metastases from a hypernephroma. I have seen cases in which these tumors were silent for thirteen years and then ran a virulent course, in spite of the fact that hypernephroma generally metastasizes early.

May we see the x-ray films?

DR LAURENCE L. ROBBINS: We have the good fortune of having the original films that were taken at the onset of the illness. They show the beginning of the lesion in the left upper lobe. Films taken while the patient was in the hospital show a considerable increase in the process. It first started as a rather nodular lesion, suggesting a multiplicity of nodules. By the time of admission there had been involvement of the lingular and lateral branches of the left upper lobe. There was some collapse, and the process was located in the anterior portion of the upper lobe. So far as could be determined at the original examination, the right upper-lung field was clear, and on the second examination it was essentially so, by the time the patient entered the hospital, however, there was evidence of something abnormal in the right upper lobe. I put up this film of the abdomen because it shows the scoliosis that was noted. There is a shadow in the region of the right kidney, which is not unusual, since after the kidney has been removed a shadow is frequently seen, suggesting that the kidney is still there — apparently, the area fills in with blood and the perirenal fat persists. I do not see the shadow of the psoas muscle, possibly because of the scoliosis.

DR DONALD S. KING: The dates of these films are interesting.

DR ROBBINS: This first film was taken in April, 1945, and the next series in March, 1946.

DR AUB: The indefinite lesion in the right apex was probably important, but I shall neglect it because I do not know what it is. The danger in not making a diagnosis of hypernephroma is that such a tumor often metastasizes to the lung, one should not make the mistake of neglecting it, saying that the lesion in the lung is a new one. It is probably unwise to do so, but I am going to do just that. The reason I do not believe that this was hypernephroma is that the position of the lesion was unusual for that diagnosis. The facts that sway me are that it was a single lesion, that it had been present for a year, that it started fairly near the hilus and extended along lines that look like the bronchi, and that the lung had collapsed peripheral to the tumor, suggesting that the lesion had occluded a bronchus rather than being out in the alveoli originally. I think that this man had infection in the collapsed upper lobe beyond the occluded bronchi. I have not forgotten, as I pointed out above, that patients with hypernephroma are likely to have fever without apparent infection. I think that this man had a primary bronchiogenic neoplasm, which may well not have been found at bronchoscopy because it was in a location difficult to see. As a matter of fact, I should not be surprised to hear that this had been caused by a metastasis from the hypernephroma — indeed, I consider it highly likely that it was. That is my second guess.

in the motor nuclei of the brain stem, even in severe and fatal cases with extensive microglial proliferation and perivascular infiltration in the same nuclei.

The anterior-horn cells of the spinal cord, for some reason, are particularly vulnerable. In another case all the anterior-horn cells on both sides were destroyed, whereas the cells of the columns of Clarke were intact. In the same case, in which death occurred five weeks after the onset, the cells had degenerated in a posterior root, presumably indicating degeneration of cells of a posterior spinal ganglion. Involvement of the ganglions or of the ganglions and posterior roots, probably explains the radicular type of pain that is often present in the early stages of the disease.

CASE 33012

PRESENTATION OF CASE

A forty-seven-year-old credit manager was admitted to the hospital with a history of cough.

Four months before admission, the patient had caught a "cold," following which a cough had persisted intermittently. He raised moderate amounts of foamy sputum with occasional flecks of bright-red blood. There were four febrile episodes, each lasting for about a week, during which the cough and sputum were accentuated. In the afternoons the temperature rose to 101 and occasionally to 103°F, with chilly sensations but no shaking chills. During this period the patient lost 15 pounds in weight. There had been a feeling of soreness and occasionally of pain in the left upper anterior portion of the chest that in the last three days before admission had become pleuritic. At the onset of the cough x-ray examination had revealed what was called a "tumor" in the left upper portion of the lung, and bronchoscopy had disclosed only inflammation, according to the patient. A month before admission another x-ray film revealed the same findings, and arrangements were made for admission to the hospital. For the next three weeks he complained of hoarseness and anorexia.

The patient had had poliomyelitis as an infant, with paralysis of the right leg and left foot and subsequent recovery except for considerable atrophy and some shortening of the right leg. He had had the usual childhood diseases, as well as typhoid fever at the age of ten. About ten years before entry, he complained of right midabdominal pain, and four years later a "hypernephroma" of the right kidney was removed. An x-ray examination of the lungs was made every three months until four years before admission, with negative findings, and the patient remained completely healthy until the onset of the present illness, except for occasional attacks of mild diarrhea.

Physical examination revealed a well developed and well nourished man. The trachea was slightly deviated to the left. There were some dullness to percussion over the left upper portion of the chest and marked diminution of breath sounds and tactile and vocal fremitus over the left upper anterior and posterior portions of the chest and apex. There appeared to be slightly less expansion of the chest on the left upper side than on the right. The voice was hoarse, and there were occasional red macules, 1 to 4 mm in diameter, on the chest. The right leg was about 2.5 cm shorter than the left. There was atrophy of the muscles of the right leg and of the left calf. There was a definite scoliosis of the spine to the right.

The temperature was 98.8°F, the pulse 92, and the blood pressure 130 systolic, 90 diastolic.

Examination of the blood disclosed a hemoglobin of 11.2 gm and a white-cell count of 23,200, with 82 per cent neutrophils, the red cells were moderately hypochromic. The urine had a specific gravity of 1.022 and gave a ++ test for albumin, with rare granular casts, 25 red cells and 2 white cells per high-power field in the sediment. The non-protein nitrogen was 27 mg, and the total protein 7.7 gm per 100 cc.

X-ray examination revealed an extensive haziness occupying the lower anterior portion of the left upper lobe, the interlobar septum was displaced forward. There was also a lobulated area of density extending upward into the midportion of the upper lobe. On the right side, there were areas of calcification in the hilus and there was haziness in the first interspace, more marked toward the axillary line. The dorsal spine showed curvature to the right, but the bones were otherwise not remarkable. A process in the right infraclavicular region had developed since previous films taken elsewhere. There was marked curvature of the upper lumbar spine, with convexity to the left and a spur formation of the right lateral margins of the vertebral bodies in this region. The skull, dorsolumbar spine and pelvis showed no evidence of metastases.

The patient developed a daily evening elevation of temperature to 102°F, with occasional pleuritic pains in the left upper portion of the chest anteriorly and a cough productive of thin, watery, mucoid sputum without blood. The chest signs remained unchanged. Penicillin had little effect on the fever. On the eighth day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. JOSEPH C. AUB: The past history suggests two diagnoses — primary tumor of the lung and metastasis from a so-called "hypernephroma" (renal-cell adenocarcinoma). Whatever the lesion was, it could have involved the recurrent laryngeal nerve. The patient had had symptoms for four years before the hypernephroma was removed. That is a long

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

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MATERIAL should be received not later than noon on Thursday, two
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COMMUNICATIONS should be addressed to the *New England Journal of
Medicine*, 8 Fenway, Boston 15 Massachusetts.

FURTHER REASONS FOR THE NURSE SHORTAGE

A LETTER appearing elsewhere in this issue of the *Journal* was prompted by an editorial, "Shortage of Nurses," that was carried in the issue of September 12. The correspondent emphasizes that the life of the nurse in training is far from ideal, particularly as it pertains to recreational and social activities. Although it has long been an accepted idea that a nurse in training should lead a life in many respects comparable to that of a nun, there is little doubt that there is no need for such an attitude to persist in this present day and generation. That his statements in this regard are generally true is open to question, on the other hand, all training schools should make a careful study to determine whether

any change in the regulations governing the social life of their students is indicated.

The remarks concerning the traditional attitude of the surgeon in the operating-room also call for careful and thoughtful consideration. Picturesque as the old-time martinet master surgeon may have been, and interesting and amusing as it may be to read of the nurses and interns as they stood cowering about the operating table of the master and unable to make any defense against his attack, it is true that all these fireworks accomplished less than nothing regarding the care these subordinates gave in the particular case on the operating table. Nor did they prevent the reoccurrence of mistakes. It is surprising to observe the quick and eager response and the gratitude that result from a few quiet words of advice and a brief explanation of what the surgeon wants, furthermore, such conduct is extremely effective in attaining the desired result in the future. With service in the armed forces so recent to many, it is worth while recalling that one rule of the Army is excellent, even though it was not by any means universally applied. "Superiors are forbidden to injure those under their authority by tyrannical or capricious conduct or by abusive language."* This regulation recognizes the absolute necessity of treating subordinates in such a manner that their self-respect is preserved, and this attitude is equally applicable to civilian life.

There appears to be no single reason for the present shortage of nurses. It would be helpful, however, if hospitals, training schools and their professional staffs would do their part in making the life of a nurse more attractive than it is at present, thereby encouraging more young women of the proper type to enter the nursing profession.

*Paragraph 3 Army Regulations 600-100

DOCTORS EAST, DOCTORS WEST

DR EDWARD H. HUME,* under the title *Doctors East, Doctors West*, has recently published the account of his establishment of the Yale Hospital in Changsha in 1906, and the later founding of the Yale-in-China school of medicine. It is a book of intense interest to any doctor concerned with the

*Hume E. H. *Doctors East, Doctors West* 278 pp. New York W. W. Norton and Company Incorporated 1946

DR KING I should like to ask Dr Castleman whether it is true that a hypernephroma often metastasizes to the lumen of the bronchus

DR BENJAMIN CASTLEMAN It metastasizes somewhat in the manner of a sarcoma. It may metastasize to the bronchus and may produce spitting of blood. Dr King and I looked up this point some years ago.

DR MALLORY We have made a diagnosis of hypernephroma on bronchoscopic biopsy in at least one case — possibly more.

What procedure was performed, Dr King?

DR KING A lobectomy. We did not do another bronchoscopy. The patient had been bronchoscoped outside the hospital, and nothing had been found. Operation seemed indicated in any event.

CLINICAL DIAGNOSIS

Metastatic hypernephroma of left upper lobe of lung

DR AUB'S DIAGNOSIS

Primary bronchiogenic neoplasm, with collapse of lung alveoli and local infection

ANATOMICAL DIAGNOSIS

Metastatic renal-cell adenocarcinoma (hypernephroma) of left upper lobe of lung

PATHOLOGICAL DISCUSSION

DR MALLORY The specimen was an interesting one. We did find a metastatic renal-cell adenocarcinoma (hypernephroma). Almost the entire tumor lay within the bronchial tree, predominantly in the branches running toward the upper portion of the lobe. They appeared to be completely obstructed by plugs of tumor tissue, but the obstruction could not have been complete because the pulmonary tissue beyond the obstruction was not collapsed but was emphysematous. The alveoli were uniformly dilated, as they are in bronchial asthma or other conditions in which there is incomplete obstruction of the bronchus. There was an area of chronic pneumonitis of considerable size near the base of the lobe, but the bronchi leading to that area were not obstructed, so that although Dr Aub's logic is excellent, the specimen does not bear it out in any way.

DR AUB I should have discussed that because the x-ray films showed the neoplasm in areas where there was perfectly good aeration and did not indicate neoplasm in the areas where there was collapse.

DR KING We should probably have operated even if we had known it was hypernephroma, in the hope that we could rid the patient of metastases. There is the famous case of the patient who is living twelve years after the removal of such a pulmonary metastasis by Dr Churchill.^{1,2} That is one reason why we went ahead and tried to find x-ray evidence of metastases before operation — we could not find it.

Three weeks after operation the patient came in to the office with severe pain in the neck requiring morphine. In addition, he had a soft-tissue mass on the top of the head, x-ray examination showed a bony defect in the skull. He returned to the hospital, and gradually the pain went away. Later the mass on the top of the head disappeared. He had one convulsion and paralysis of the right leg, the paralysis also cleared. At present, several months after operation, the patient is better than he has been for a long time. I do not know what became of the soft-tissue mass in the scalp.

DR MALLORY Had any x-ray treatment been given, Dr Robbins?

DR ROBBINS Not so far as I know.

DR KING The patient was not given any, he had received some stilbestrol but only for a few days. It upset his stomach and was consequently discontinued.

DR ROBBINS This is the film taken prior to operation. I do not know whether you can see the definite defect in this portion of the parietal bone — it has disappeared since the original film. There was an area of approximately 2 cm. in length involving the outer table. The inner table is well preserved.

DR ALLEN G. BRAILEY What was the cause of the signs in the right apex?

DR KING More metastases, but we have not taken an x-ray film since then.

DR MALLORY The patient was placed on penicillin six days before operation, with quite a marked effect on the temperature chart. The day after operation the temperature dropped to normal. We still do not know whether the fever was due to pneumonitis or to the hypernephroma.

DR AUB Does hypernephroma cause fever without any other obvious cause?

DR MALLORY Unquestionably.

DR AUB This is another example of the fact that one should always pick out the obvious diagnosis.

REFERENCES

1. Barney, J. D. and Churchill, E. D. Adenocarcinoma of kidney with metastasis to lung cured by nephrectomy and lobectomy. *Tr. A. Genito-Urin. Surgeons* 31:71-79, 1938.
2. Barney, J. D. Twelve year cure following nephrectomy for adenocarcinoma and lobectomy for solitary metastasis. *J. Urol.* 57:406, 1944.

program to include every Massachusetts resident as soon as possible

In order to ensure a fair distribution of the whole blood that is currently available, the following priority system has been set up *first priority* includes actual donors and members of their immediate families, *second priority* is given to residents of communities in which the Mobile Unit has taken blood, *third priority* goes to residents of communities in which the Mobile Unit is definitely scheduled to visit, and *fourth priority* takes in all other residents of Massachusetts. Emergency cases are given first consideration anytime that the required type of blood is on hand

SCHEDULE FOR MOBILE-UNIT VISITS

The Mobile Unit of the Massachusetts Blood Donor Program will make the following visits in the near future

PLACE	DATE
New Bedford	January 27, 28 and 29
Stonham	January 31

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR NOVEMBER, 1946

RÉSUMÉ

DISEASES	NOVEMBER 1946	NOVEMBER 1945	SEVEN-YEAR MEDIAN
Anterior poliomyelitis	55	46	10
Chancroid	2	1	*
Chicken pox	770	771	1025
Diphtheria	61	17	17
Dog bite	664	651	592
Dysentery, bacillary	3	9	24
German measles	63	55	55
Gonorrhea	378	509	426
Granuloma inguinale	0	0	*
Lymphogranuloma venereum	15	44	*
Malaria	691	657	816
Measles	6	7	12
Meningitis meningococcal	5	5	3
Meningitis Pfeiffer-bacillus	1	5	4†
Meningitis pneumococcal	1	0	0†
Meningitis staphylococcal	0	1	0†
Meningitis streptococcal	1	0	1†
Meningitis other forms	1	3	5†
Meningitis undetermined	306	523	523
Mumps	61	92	225
Pneumonia, lobar	14	7	5
Salmonella infections	294	466	704
Scarlet fever	301	391	419
Syphilis	227	241	215
Tuberculosis pulmonary	12	9	16
Tuberculosis other forms	3	3	2
Typhoid fever	5	4	4
Undulant fever	598	661	661
Whooping cough			

*Made reportable December 1943

†Four year average

COMMENT

Diseases reported at an incidence above the seven-year median included anterior poliomyelitis, diphtheria, German measles, malaria, Salmonella infections, typhoid fever and tuberculosis

Diseases reported at an incidence below the seven-year median included chicken pox, bacillary dysentery, measles, meningococcal meningitis, mumps, lobar pneumonia, scarlet fever and whooping cough

Diphtheria was reported at the highest prevalence for this month since 1933, being three times that of the corresponding month of last year

Poliomyelitis continued to occur much later than usual, resulting in a higher number of cases for the month than in 1945, although the total cases for the year to date is much lower

Lobar pneumonia continued to manifest the lowest incidence for this month, being less than one fourth that of the seven-year median. It again shattered the all-time record

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anterior poliomyelitis was reported from Arlington, 1; Ashburnham, 8; Athol, 1; Boston, 5; Brookline, 2; Dover, 1; Easthampton, 3; East Bridgewater, 1; East Longmeadow, 1; Everett, 1; Falmouth, 1; Fall River, 1; Ipswich, 1; Lowell, 1; Lynn, 5; Milton, 1; Needham, 1; New Bedford, 1; Newton, 6; Orange, 1; Randolph, 1; Somerville, 1; Springfield, 1; Swampscott, 1; Upton, 1; Watertown, 1; Weston, 2; Worcester, 4; total, 55

Diphtheria was reported from Arlington, 1; Billerica, 1; Boston, 17; Brockton, 1; Cambridge, 2; Chelsea, 3; Dedham, 2; Easthampton, 1; Lowell, 3; Lynn, 1; Marlboro, 1; Medford, 2; New Bedford, 1; Newton, 1; Palmer, 1; Randolph, 3; Somerville, 14; Watertown, 2; Westboro, 2; Woburn, 1; Worcester, 1; total, 61

Dysentery, amebic, was reported from Murphy General Hospital, 1; total, 1

Dysentery, bacillary, was reported from Boston, 1; Worcester, 2; total, 3

Encephalitis, infectious, was reported from Haverhill, 1; North Adams, 1; total, 2

Malaria was reported from Amesbury, 1; Boston, 7; Leominster, 1; Montague, 1; Murphy General Hospital, 3; Springfield, 1; Worcester, 1; total, 15

Meningitis, meningococcal, was reported from Boston, 1; Lowell, 1; Montague, 1; New Bedford, 1; Worcester, 2; total, 6

Meningitis, Pfeiffer-bacillus, was reported from Billerica, 1; Cambridge, 1; Fall River, 1; Medway, 1; Salem, 1; total, 5

Meningitis, pneumococcal, was reported from Everett, 1; total, 1

Meningitis, other forms, was reported from Lowell, 1; total, 1

Meningitis, undetermined, was reported from Haverhill, 1; total, 1

Salmonella infections were reported from Boston, 1; Everett, 1; Haverhill, 4; Northfield, 2; Quincy, 1; Revere, 1; Salem, 3; Wellesley, 1; total, 14

Septic sore throat was reported from Amesbury, 8; Boston, 6; Merrimack, 7; Somerville, 1; total, 22

Trichinosis was reported from Bridgewater, 1; Malden, 1; Worcester, 2; total, 4

Typhoid fever was reported from Lowell, 1; Somerville, 1; Worcester, 1; total, 3

Undulant fever was reported from Gardner, 1; Northfield, 1; Quincy, 1; Southampton, 1; Worcester, 1; total, 5

CORRESPONDENCE

SHORTAGE OF NURSES

To the Editor: Reading the editorial "Shortage of Nurses" in the September 12 issue of the *Journal* was stimulus sufficient to make for finding and reading the editorial in the July 11 issue of the *Journal* and the editorial "The Training of the Graduate Nurse" in the July issue of the *Virginia Medical Monthly*

These articles take cognizance of the shortage of nurses, and in one it is suggested that the situation is a consequence of increasing educational requirements demanded for the registration of graduates. The seriousness of this state of affairs is apparent to all in the medical profession, and therefore needs no further comment

The motive for this letter came from the conviction that one obvious source of information had been neglected, that is the student nurse herself. Accordingly, I have, in the past few months, spoken to many nurses, attempting to unearth reasons why the profession is no longer so desirable as it once was

The major criticism was directed at the training itself. Graduates frequently said that if they had the choice to make again they would certainly not go into nursing training. A paradox was pointed out in that only girls whose high-school records indicated superior ability were accepted by the training schools of the better hospitals. Yet the demands on the trainees in these hospitals precluded learning to a large degree. Learning, it was thought, stopped almost entirely after the first year, for thereafter the hospitals seemed so bent on exacting the worth of the food and lodging supplied the trainee in actual work mass that a state of chronic fatigue

extension of his art and science, and to the student of Chinese ways and culture and history

It was only two years after the treaty opening Hunan Province to foreigners, and only five years after the memorable Boxer Rebellion, that Dr Hume entered what had been virtually a forbidden city, a year later he opened the Yeh Hospital, and waited for Yale's first patients in China. The story of the hospital's early days in the community and the place that it eventually found for itself, the starting of the medical school, the erection of new buildings, the Harkness gift and the eventual turning over of the Hsiangya Medical Educational Association to the provincial government make fascinating reading.

The substance of the book, however, is in the title, for its real story is of the meeting of Occidental with Oriental medical culture, and the lessons that each had to learn. According to a Chinese proverb,

**To read the medical classics exhaustively
Is not equal to frequent visits to the sick,**

and as some evidence of the value of this advice we find published about the year 196 A D. a treatise on typhoid fever by Chang Chungching, giving an accurate clinical description of the disease, with the advice to avoid violent purgatives in its treatment and to reduce the fever with cooling baths. Seaweed extracts for the treatment of certain kinds of goiter are recommended in classic Chinese medical literature, and fish-liver oils for tuberculosis, inoculation against smallpox was practiced from early times. One of the most interesting examples of Chinese medical perspicuity is found in the story of a Western woman treated unsuccessfully for pernicious anemia by Sir Patrick Manson in Amoy. Later a Chinese physician of the old school offered to cure her — and did — with large doses of crow's liver, decades before modern medical science had discovered the liver treatment of the disease!

Dr Hume tells of his consultation with Dr Wang, of the old school, and of their mutual arrival at the same diagnosis by different methods, for

**By nature men are nearly alike,
Their customs differ widely,**

and of his invitation to Dr Wang to give a course of lectures on the old art at the new medical school.

This was, indeed, the attitude that particularly fitted the author for his post, for

**He who looks back to the old
And knows the new
Is worthy to be a scholar**

MASSACHUSETTS MEDICAL SOCIETY BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups, such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of dates can be avoided.

DEATHS

BERGERON — George G. Bergeron, M.D., of Ludlow, died September 26. He was in his fifty-sixth year. Dr. Bergeron received his degree from Temple University School of Medicine in 1917. He was a fellow of the American Medical Association.

SIMMONDS — Frederick J. Simmonds, M.D., of Jamaica Plain, died December 6. He was in his sixty-ninth year. Dr. Simmonds received his degree from Middlesex University School of Medicine in 1917. He was a fellow of the American Medical Association. His widow survives.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

PRIORITY SYSTEM ON FREE WHOLE BLOOD

When needed, whole blood may be obtained free by actual donors and members of their immediate families under a priority system now in effect for the Massachusetts Blood Donor Program. (Doctors and hospitals may continue to charge their usual fee for administration.)

Originally it was believed that the program could not undertake the distribution of whole blood until some time in 1947. The return of Army-Navy surplus stocks of plasma, however, enabled the Department of Public Health to supply Massachusetts hospitals with plasma from this reserve instead of using the blood from current donations for plasma production. This made it possible for the Department to turn its attention to processing fractions and developing the whole-blood phase of the program. In September, 1946, the Blood Donor Program began to furnish free whole blood for people who had actually donated to the program and for members of their immediate families. Although the distribution of whole blood has increased, there is still not enough to meet the need throughout the Commonwealth. The program is expanding steadily, however, and efforts are being made to extend the

The New England Journal of Medicine

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Volume 236

JANUARY 9, 1947

Number 2

PRESENTATION OF THE HENRY JACOB BIGELOW GOLD MEDAL

INTRODUCTORY REMARKS AND PRESENTATION OF THE MEDAL*

DONALD MUNRO, M D †

BOSTON

THE occasion of this meeting of the Boston Surgical Society is for the presentation of the Henry Jacob Bigelow Gold Medal. Tradition and custom, however, have decreed that some scientific contribution shall be made at every meeting of the Society. In consequence, the distinguished surgeon who will receive the Bigelow Medal, Dr. Frank H. Lahey, has been asked to present a paper. We are fortunate in that he has chosen thyroid surgery as his subject. He is well known to all in this audience and needs no further introduction. I have the honor of presenting Dr. Frank H. Lahey.

(Dr. Lahey then read a paper on thyroid surgery.)

The Boston Surgical Society was incorporated in November, 1914. In February of the following year, Dr. William Sturgis Bigelow presented the Society with the sum of five thousand dollars in memory of his father, Henry Jacob Bigelow, directing that the income derived from this sum of money be used from time to time for the presentation of a gold medal to be known as the Henry Jacob Bigelow Medal. The award is made for "new and valuable work in surgery or in fields connected with it." The medal was first awarded in 1921 to Dr. William J. Mayo. Since then eight other awards have been made, this present one being the tenth. The other recipients were Drs. William W. Keen, Rudolph Matas and Chevalier Jackson, Mr. George Grey Turner, and Drs. John M. T. Phinney, Harvey Cushing, Edward W. Archibald and Allen O. Whipple. Surgeons of the United States, England and Canada are represented.

The Society has been chary about awarding the medal to one of its own members, and it can be accepted as fact that before doing so it has interpreted the terms of the award with more than usual stringency. In consequence, only one member has previously received the medal. Dr. Harvey Cushing.

Tonight it gladly honors another member. Dr. Frank H. Lahey, director of the Lahey Clinic here in Boston, on the basis of his accomplishments not only in the field of surgery but also in those broader

fields that are connected with it well merits inclusion in this distinguished group of recipients. His mastery of thyroid surgery and surgery of the esophagus and bowel, for example, is but an indication of the scope of his technical skill. The presidencies of the American Medical Association and the New England Surgical Society, the governorship of the American College of Surgeons and membership, both honorary and regular, in many other surgical societies point to his great influence among the medical profession. He has held professorial posts in Harvard and Tufts College medical schools. The Lahey Clinic is famous for the opportunities it affords for graduate studies. Without his steadying influence during the war, the civilian physician situation would have been a serious menace to the public health. Even now, his influence is being continually exerted as a member of the Presidential Advisory Committee on the Integration of Medical Services in the Government to the end that, among other things, the veterans shall receive better care.

Nor should we forget in honoring Dr. Lahey to do equal honor to Mrs. Lahey. All in this audience know what profound influence a surgeon's wife exerts on the surgeon. Without her sustaining aid his courage would many times falter, without her encouragement he would never be inspired to rise to heights believed by him to be beyond his reach. She puts up with long lonely hours, a frequently disrupted household and those temperamental peculiarities that are characteristic of a person who by nature and by training is above all things an individualist. Dr. Lahey will, I am sure, agree with me that without the devoted and loyal support given him by Mrs. Lahey he would never have achieved even a modicum of the deserved success that has been his.

Dr. Lahey—superlative surgeon, doctor who teaches doctors, redoubtable administrator, adviser of Presidents in war and peace and, above all, a man who has the courage to be honest with himself—as the representative of the Boston Surgical Society I take great personal pleasure in having the honor to present to you in its name the Henry Jacob Bigelow Gold Medal.

*This and the succeeding paper comprise the addresses delivered at the presentation of the Henry Jacob Bigelow Gold Medal at a meeting of the Boston Surgical Society, Boston, May 10, 1946.

†President, Boston Surgical Society.

supervened. This prohibited intelligent reading, attention at lectures vacillated. Regarding duties, a tendency toward automatism became increasingly great and interest waned in why a patient with a given disease received a particular kind of therapy. Initiative succumbed as the consciousness of not learning became engulfed in a despair at being able to learn.

The attitudes of physicians toward students were often thought to be not that of gentlemen. Cursing, harsh words, incessant satire all were mentioned, frequently with rancor. Few doctors ever troubled to explain what was being done or why it was being done — as in the operating room, where the student worked for weeks watching operations designed to accomplish she knew not what, on patients she knew nothing of.

The social restrictions of a trainee's life weighted heavily with every nurse consulted. It seemed not at all clear to them as trainees, why they should lead cloistered lives. They are allowed liberty until midnight on five nights each month, whereas girls of comparable age in colleges or in their homes are considered mature enough to decide how often and how long social activities should be indulged in. An incongruity is manifest when this attitude is referred to a nurse's responsibilities with a seriously ill patient.

Finally, it was pointed out that following graduation, a registered nurse could expect a job working for more than eight hours at various times during the twenty-four hours of the day. Exposure to all the ills of mankind would be her lot, and for this she would receive less money than many secretaries — special duty nurses, it was admitted, do far well financially.

These thoughts were garnered in talking with nurses at the various hospitals to which students in the Harvard Medical School are assigned. I think that they certainly are valid and active reasons why there is a shortage of nurses. An examination of training-school statistics will reveal that some classes lose as many as 50 per cent of their original enrollment — admittedly, not all losses are due to the defects in the character of the training as described.

Succinctly, it is fair to say that from the point of view of the nurse, the shortage of nurses could in large measure be repaired by making the life of a student nurse more attractive — that is, by devoting more of the required three years to teaching and less of it to drudgery, by a real effort on the part of hospital staffs to improve attitude and conduct toward trainees, by attributing to student nurses a degree of maturity enjoyed by comparable groups of young women and by providing more nearly adequate recompense for graduates.

PAUL D. HOEPRICH

125 Parker Hill Avenue
Roxbury 20, Massachusetts

BOOK REVIEW

A Bibliography of Infantile Paralysis, 1789-1944. With selected abstracts and annotations. Prepared under the direction of The National Foundation for Infantile Paralysis, Incorporated. Edited by Morris Fishbein, M.D. Compiled by Ludvig Hektoen, M.D. 4th ed., cloth, 672 pp. Philadelphia: J. B. Lippincott Company, 1946.

A bibliography of infantile paralysis has long been needed by the medical profession, librarians, public-health officials and the public at large. The subject has grown to vast proportions, and Dr. Ludvig Hektoen and his associates, under the general editorship of Dr. Morris Fishbein, have compiled and annotated over eight thousand selected references for the National Foundation for Infantile Paralysis. The book is more than a list of papers, for the most important references have been carefully evaluated and a brief summary, usually less than six lines in length, gives the essential material contained in the article, sometimes disclosing facts that are not implied in the title of the paper. It is this aspect of the bibliography that makes the book of particular importance to the medical profession.

Beginning with the paper by Underwood in 1789, the bibliography continues through the year 1944. There are a full index of authors and a subject index giving references to the many aspects of poliomyelitis that have been investigated in the past. Thus, one can readily find out the most significant references to such subjects as facial-nerve paralysis in poliomyelitis, flies as carriers of the disease, seasonal in-

cidence, the cerebellar form of poliomyelitis, the involvement of the cerebrospinal fluid, chronic anterior poliomyelitis, quarantine, Theiler's virus and the relation of tonsillectomy to poliomyelitis.

The book is a good example of co-operative research by a chief editor and a fully qualified medical reference librarian. It can be recommended without question as a standard work. The volume is singularly free from error, usually complete and clearly printed, with two indexes that are among the best that have ever been assembled. The editor and the compiler are to be congratulated on the publication of an outstanding work on infantile paralysis.

NOTICES

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, February 7, 1947.

Arrangements will be made, so far as is possible, for candidates to take the Part I examination (written paper and submission of case records) at places convenient for them. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held June 1-7, 1947, at Pittsburgh. Notice of the exact time and place of the Part I and Part II examinations will be sent to all candidates well in advance of the examination date.

For further information and application blanks address Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh 6, Pennsylvania.

PUBLIC-HEALTH FELLOWSHIPS FOR PHYSICIANS AND ENGINEERS

Announcement is made by Surgeon General Thomas Parrish of the United States Public Health Service that applications for fellowships in postgraduate public-health training for physicians and engineers for the school year beginning in the fall of 1947 will be received at any time prior to May 1, 1947.

The fellowships are made possible by a grant of \$228,400 from the National Foundation for Infantile Paralysis through funds contributed to its "March of Dimes." Fifty-three students were awarded fellowships for the school year beginning in September, 1946.

The fellowships provide graduate training of approximately nine months in an accredited school of public health or an acceptable school of sanitary engineering, followed by three months of field training, and are open to men and women, citizens of the United States, under forty-five years of age. Physician applicants must have completed at least a year's internship. Engineering graduates with a Bachelor's or higher degree in sanitary, civil or chemical engineering are eligible, and those with other engineering degrees who have had experience in the public-health or sanitary engineering field may also submit applications.

The specific purpose of the fellowships is to aid in the recruitment of trained health officers, directors of special services and engineers to help fill hundreds of vacancies existing in state and local health departments throughout the country. The fellowships are intended for newcomers to the public health field and are not open to employees of state and local health departments, for whom federal grant-in-aid funds are already available to the states.

Applicants for fellowships may secure further details by writing to the Surgeon General, United States Public Health Service, 19th and Constitution Avenue, N. W., Washington 25, D. C., Attention: Public Health Training.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JANUARY 9

FRIDAY, JANUARY 10
 9:00-10:00 a.m. Sterility Dr. Somers Sturgis Joseph H. Pratt
 Diagnostic Hospital
 10:00 a.m.-12:00 p.m. Medical Staff Rounds Peter Bent Brigham Hospital
 12:00 m.-1:00 p.m. Clinicopathological Conference (Boston Floating Hospital) Joseph H. Pratt Diagnostic Hospital

(Notices continued on page xv)

uch we are greatly indebted to Dr E B Astwood, no longer need surgeons fear even the seriously toxic patients with hyperthyroidism in whom, in the first, multiple-stage procedures were frequently necessary.

Because thiouracil, thiobarbital and propylthiouracil so positively and dependably bring the metabolic rate to normal in patients seriously affected by hyperthyroidism because these danger-

quickly than several men, acquires familiarity with the advantages and dangers related to the administration of this useful drug in preparing patients with hyperthyroidism for surgery.

In an article on this subject published by the Clinic,¹ a simple diagram (Fig 2) was employed to illustrate the origin of hyperthyroidism, together with what has been suggested by many as the possible way in which these drugs bring about a

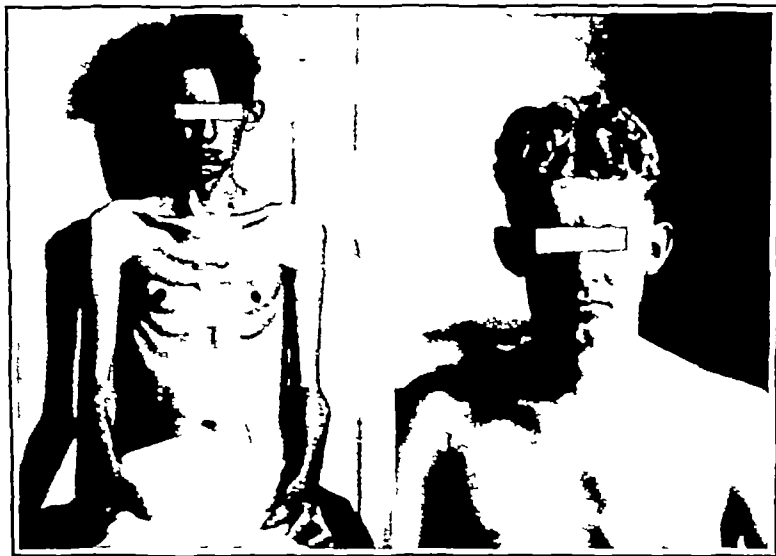


FIGURE 1 Photographs of Patient with Severe Hyperthyroidism before and after Operation. The photograph on the left shows the extreme degree of emaciation that can result when the disease is untreated, that on the right shows the normal state that was attained after subtotal thyroidectomy.

ous but useful drugs will abolish multiple-stage procedures in the surgery of hyperthyroidism, because they will still further reduce, if not abolish the already low mortality, — a patient mortality of 0.88 and an operative mortality of 0.73 per cent, as compared with a patient mortality of 0.17 per cent with the use of these agents, — and because we have now employed these drugs in preparing for surgery over 500 patients with hyperthyroidism, it is important to report our experience with them. Because these powerful controllers of thyroid hyperactivity have real dangers, as well as real advantages, some of their complications are discussed.

Desiring to concentrate experience with these dangerous drugs in the hands of one man so that he could have the largest possible experience with them, we have turned over their administration in the preparation of patients with hyperthyroidism for surgery at the Clinic to Dr Elmer C Bartels. By this plan, which I recommend for any hospital using this dangerous drug in the treatment of patients with hyperthyroidism, one man, much more

return of the elevated basal metabolic rate to normal and thus abolish the symptoms of hyperthyroidism associated with the elevated metabolic rate.

Early in our experience in operating on patients with hyperthyroidism who had had their metabolic rates brought to normal by these drugs, we became distressingly aware of the fact that, although the patients were freed from toxicity, the thyroid glands themselves were in the same state as those before the introduction of Lugol's solution by Dr Henry S Plummer to prepare the patients for surgery. The thyroid glands of patients prepared with thiouracil alone were friable and vascular and did not hold double hooks, ligatures cut through, bleeding was almost uncontrollable, and microscopic section — in spite of the fact that these patients were free from toxicity — showed the glands still to be markedly hyperplastic, including all the features found in patients with severe hyperthyroidism untreated with iodine.

As may be seen in Figure 2, the effect of thiouracil, as has been suggested by many, is an extrathyroid

SURGERY OF THE THYROID GLAND*

FRANK H LAHEY, M D †

BOSTON

I HAVE selected the subject "Surgery of the Thyroid Gland" because the Lahey Clinic and I have literally grown up almost from the beginning of the developments in this field and have had a hand in bringing about some of them, because this experience represents almost as large an acquaintance with the subject as exists in the world today and has therefore made available to us a considerable knowledge of the unusual thyroid states with which men not dealing with these conditions daily are often not familiar, because it is particularly appropriate to present a review of this special experience in the community in which it has been had and to a group of surgeons with whom I have lived and who have been my friends and colleagues and, finally, because in the audience to which it is presented are many of my lay friends who I hope will be able to understand and be interested in at least more of the aspects of this review than would be true of a perhaps more erudite but less dramatic subject.

Since this presentation is in the nature of a review and a report on this experience, the material represents the work of many men in the Clinic, much of which has been published in special papers on the various individual aspects of thyroid disease. Because the subject lends itself so well to illustrative demonstration, each aspect is demonstrated, so far as possible, by illustrations, making it, I hope, additionally comprehensible to the nonprofessional portion of the audience.

This review is based on an operative experience with between 25,000 and 26,000 thyroid operations on between 22,000 and 23,000 patients with thyroid disease (Tables 1 and 2). Since this paper deals

absence of the thyroid gland and other nonsurgical thyroid states.

The developments in this disease are discussed not only from the standpoint of better management in its various aspects but also to demonstrate progress in the attempt to educate the family physician, who first sees these patients, to deal with them more aggressively and at an earlier stage, before they have reached advanced degrees of emaciation and intoxication.

I have purposely selected two old photographs (Fig 1) to demonstrate the state of intoxication to which these patients with hyperthyroidism were in the past often permitted to go, and, in the same patient, the result following subtotal thyroidectomy. This is also a graphic demonstration of what hyperthyroidism actually is. Hyperthyroidism, as can be

TABLE 2 Mortality following Thyroidectomy

Number of operations	25,000
Operative mortality	0.75%
Number of patients	22,000
Patient mortality	
All cases	0.83%
Cases since July 1, 1943	0.37%
Cases during 1945	0.17%

seen from these two illustrations preoperatively and postoperatively, is a disease brought about by hypermetabolic activity, stimulated, in turn, by the excessive synthesis of thyroxine. It is now well known that the excessive synthesis of thyroxine causes the weight loss dramatically illustrated in Figure 1, which is only the external evidence of the unseen but real effects of excessive metabolism on inner, nonvisible structures, such as the liver, the heart, the epiphyseal centers in young children, the intestinal tract and the retro-ocular muscles and fat, that play a large part in intractable exophthalmos (see Figs 7, 8, 12, 17, 18 and 19).

The introduction of iodine in the preparation of patients for subtotal thyroidectomy for hyperthyroidism, together with the improvement in technical procedures and in anesthesia and the better preoperative preparation and postoperative care of these patients, has resulted in such a lowering of mortality rates that the family physician no longer delays recommending operation until the patients have reached the states shown in Figure 1.

Thiouracil, Thiobarbital and Propylthiouracil

As the result of the development of the use of thiouracil, thiobarbital and propylthiouracil, for

TABLE 1 Types of Thyroid Disease

Disease	No. of Cases
Hyperthyroidism including primary hyperthyroidism and adenomatous goiter with secondary hyperthyroidism	16,000
Nontoxic goiter	9,000
Total	25,000

particularly with the surgical treatment of thyroid disease, no mention is made of other states that rarely require surgery, such as diffuse colloid goiter, endemic and nonendemic, thyroiditis of the Riedel's struma type and of the Hashimoto's struma lymphomatosa type, lingual goiter, sublingual goiter, thyroid tuberculosis, syphilis and abscess, unilateral

*From the Department of Surgery, Lahey Clinic.

†Director, Lahey Clinic.

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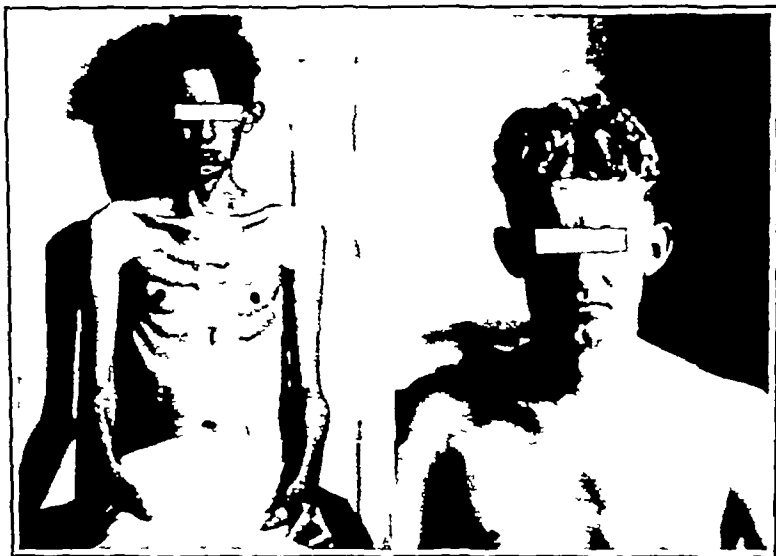


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As may be seen in Figure 2, the effect of thiouracil, as has been suggested by many, is an extrathyroid

one, possibly on inorganic iodine, which the thyroid gland synthesizes into organic iodine, either by so affecting the iodine that it is no longer satisfactory for synthesis or by its effect on the proteolytic action of the gland so that organic iodine (thyroxine) is no longer synthesized.

If iodine is no longer synthesized into thyroxine, one can understand what Bartels² has observed in patients with hyperthyroidism to whom one of these three drugs had been administered with reasonable regularity one can assume that, to bring the metabolic rate to normal, a full dosage of these drugs (0.6 gm of thiouracil, 50 mg of thiobarbital or from 175 to 225 mg of propylthiouracil) will take approximately the number of days that the metabolic rate has been above normal. This finding

tion brought about in the patient shown in Figure 1 by the administration of Lugol's solution and demonstrates the dilatation of the acini and the compression of the epithelial cells lining the acini. This is called "involution effect" brings about devascularization, firmness and almost ideal operating conditions.

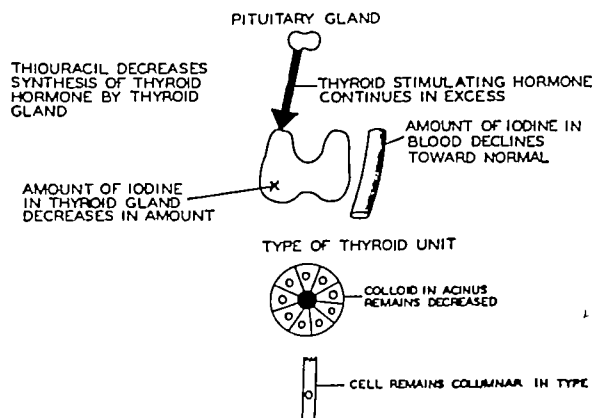


FIGURE 2 Physiologic Changes in Primary Hyperthyroidism following Thiouracil Therapy

Thiouracil brings about the return of the basal metabolic rate to normal and abolishes the symptoms of hyperthyroidism without changing the histologic picture of hyperthyroidism within the gland and without inhibiting the pituitary-stimulating hormone, which incites the hyperplasia within the thyroid (reproduced from Lahey et al¹ by permission of the publisher)

is predicated on the reasonable basis that this period represents the time necessary to use up the thyroxine already manufactured and stored in the tissues and in the thyroid gland, it has been demonstrated that these drugs have no effect on the efficacy of thyroxine already manufactured and that their effect is only in preventing the synthesis of more thyroxine.

Figure 3 shows a high-power photomicrograph of the friable, high-columnar epithelial cells lining the acini in the hyperplasia associated with the overactive thyroid gland of hyperthyroidism untreated with iodine. This type of hyperplasia is seen in patients with hyperthyroidism whose metabolic rate has been brought to normal with thiouracil, thiobarbital or propylthiouracil and in whom, because of this persisting hyperplasia, operating conditions are unsatisfactory. Figure 4 illustrates the involu-



FIGURE 3 High-Power Photomicrograph of the Columnar Epithelial Cells Lining the Acini

This is the histologic picture found in the patient with hyperthyroidism whose metabolic rate has been brought to normal with thiouracil; it demonstrates why the thiouracil-prepared thyroid gland bleeds so excessively.

in patients prepared for surgery with Lugol's solution.

Because of the undesirable operating conditions in patients with hyperthyroidism prepared solely with thiouracil, thiobarbital or propylthiouracil, Dr. Bartels and I have devised a plan combining the advantages of thiouracil and iodine. Figure 1 demonstrates the typical course, with a drop in the basal metabolic rate and a gain in weight, in a patient with hyperthyroidism during the period in which thiouracil was administered and in the final three-week period during which iodine was administered, the desirable effects of both drugs being obtained. By this means it is possible to prepare patients with severe hyperthyroidism for surgery so that ideal operating conditions are established. The metabolic rate is brought to normal, the symptoms of hyperthyroidism disappear and the gland is converted into an avascular, firmly involuted one that can be managed technically with complete satisfaction.

Table 2 presents the patient and the operative mortality in our entire series of thyroid operations,

arting with the period from our very first case and cluding the period when we had had relatively the experience with the disease, as well as the



FIGURE 4 Low-Power Photomicrograph of Thyroid Gland This demonstrates involution brought about by the intrathyroid effect of iodine and shows the dilatation of the acini, the compression of the epithelial cells lining the acini and the production of firmness and devascularization, which furnish ideal operating conditions

period before iodine was used in the preparation of the patients. The patient mortality for the entire series was reduced from 0.88 per cent on July 1,

patient who died of coronary disease. During this period no multiple-stage operations were performed. The average stay in the hospital has decreased from fifty-five days in patients prepared with iodine who required three-stage operations and thirty-five days in patients prepared with iodine who required two-stage operations to eight days in patients prepared with one of these three drugs.

In 100 patients with severe hyperthyroidism treated with one of these three drugs, Bartels² has shown that the average basal metabolic rate was +49 per cent before treatment and +7 per cent after treatment and that the average weight loss before treatment was 25 pounds and the average weight gain after treatment, 12 pounds.

Complications occurring with the administration of these drugs can be — and have been — of a serious character. They consist of various degrees of neutropenia and granulocytopenia, fever, skin eruptions and enlargement of the salivary glands. Dr. Bartels has demonstrated that these complications can be anticipated in 9 per cent of patients treated with thiouracil and in 28 per cent of patients treated with thiobarbital. We have now operated on 60 patients prepared with propylthiouracil, with 100 others in preparation for surgery. Propylthiouracil has not as yet been employed long enough and in large enough doses to be certain of its complications. Two patients have already shown marked depressions of the white-cell count, in 1, the white-cell count was reduced to 1900, with no neutrophils. We strongly suspect that although propylthiouracil may produce fewer complications than the other

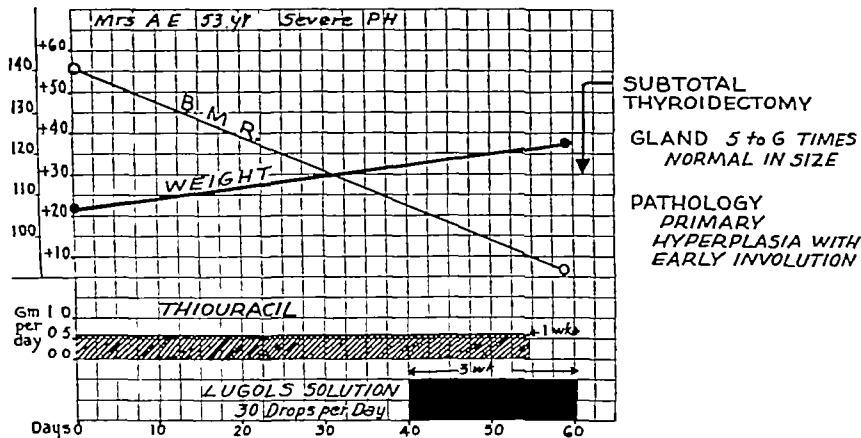


FIGURE 5 A Plan for the Preoperative Preparation of Patients with Hyperthyroidism by the Combined Use of Thiouracil, Thiobarbital or Propylthiouracil and Iodine It should be noted that Lugol's solution is given during the last three weeks of preparation, bringing about involution and ideal operating conditions. No thiouracil is given for the last week before operation because of the fact that agranulocytosis has occasionally been found to occur as late as seven days after the last dose of such drugs, a complication that would be undesirable either at the time of operation or during postoperative recovery (reproduced from Bartels² by permission of the publisher)

1943, when thiouracil was first used in the Clinic, to 0.27 per cent, and the patient mortality for the year 1945 was but 0.17 per cent, representing a

two drugs, it will prove capable of causing death if given in doses adequate to reduce the metabolic rate to normal (equivalent to 0.6 gm of thiouracil)

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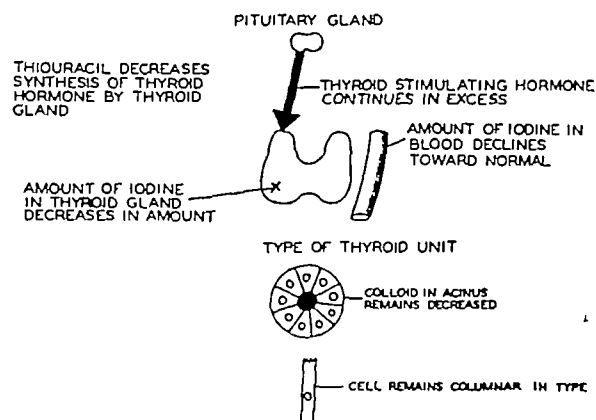


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Apathetic Hyperthyroidism

Because a chronic type of hyperthyroidism of low grade that frequently occurs in older people, to which I gave the name "apathetic hyperthyroidism" some years ago, is often overlooked, being different from the typical activated hyperthyroidism shown in Figure 6, I call attention to the existence of this atypical type, illustrated in Figure 7

I gave the name apathetic hyperthyroidism to this condition, not with any idea that it represented any special group but merely to call attention to the fact that there is a type of hyperthyroidism without eye signs, without activation, without marked enlargement of the gland and with only moderate tachycardia but particularly associated with marked weight loss and marked myasthenia over a long period and that because of the lack of these outstanding signs this type of hyperthyroidism is often overlooked. I also called attention to the fact several years ago that this type of hyperthyroidism, which is frequently associated with only moderate elevations in basal metabolic rates, is often approached too confidently by the surgeon because it does not have striking signs of overactivation, the condition is not given the attention and caution warranted by the reactions and fatalities that can occur following surgery in this type of hyperthyroidism.

I am sure, as I have repeatedly written, that there are many patients with such a low grade of this type of chronic hyperthyroidism, exhibiting such unstriking evidences of disease, who are undiagnosed in many communities. It is in these patients that proper preoperative preparation and subtotal thyroidectomy can achieve some of the most brilliant results in the surgery of hyperthyroidism.

Thyrocardiac Disease

Figure 8 shows a preoperative and postoperative view of a patient belonging in the group of thyroid conditions to which Hamilton and I³ gave the name thyrocardiac. It was with Dr. Hamilton's aid and

thyroidism⁴. It will be noted in this diagram, devised by Dr. Hurxthal, that in the patients with any limited cardiac capacity, the superimposed needs of increased circulation rate associated with an increased metabolic rate cannot be met by a compensatory increase of the circulation rate with an inadequately capable heart, the section illustrating the high metabolic rate with only a normal uncompensating circulation rate demonstrates why failure occurs and how it is possible, by means of subtotal thyroidectomy, which brings the metabolic



FIGURE 8 Photographs of a Thyrocardiac Patient before and after Subtotal Thyroidectomy

Before operation (a) there were anasarca and ascites. After operation (b) there were restoration of compensation and relief from hyperthyroidism.

TABLE 3 Follow-up Data in 614 Patients Operated on for Thyrocardiac Disease (1922-1941)

Patient untraced	143
Patient dead	165
Patient alive	
Grade I result	201
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Figure 9 graphically demonstrates why cardiac decompensation occurs in patients with hyper-

rate to normal, or by means of the administration of thiouracil, thiobarbital or propylthiouracil, which brings the metabolism to normal, to bring the circulation rate and metabolic rate into balance, with restoration of compensation. Figure 10 shows the cardiac shadow in a thyrocardiac with failure and the return of the cardiac shadow to normal following the elimination of the hyperthyroidism by subtotal thyroidectomy as graphic evidence of this accomplishment.

Table 3 presents the number of patients, of a total of 306 known to be living, who have obtained Grade I, Grade II and Grade III results among those who have been followed postoperatively for varying periods from 1922 to 1941. Grade I repre-

Dr Bartels has demonstrated that if these complications occur and the drugs are stopped and again administered, there will be an increased hazard of recurrence. He has also shown that agranulocytosis and neutropenia can occur up to seven or eight days after withdrawing the drug and as late as the ninth month after beginning treatment and on a dose as low as 0.2 gm of thiouracil. It is for these reasons that no thiouracil, thiobarbital or propylthiouracil is given for a week before the patient comes to operation (Fig 5), to avoid the coincidental occurrence of one of these states with the operative procedure or postoperative recovery.

When agranulocytosis and neutropenia — the most dangerous of all these complications — have occurred, no treatment can compare in usefulness with that of penicillin in large doses. Pyridoxine, vitamin B-6 and liver extract are administered together with penicillin, but penicillin is the single measure on which the greatest dependence can be placed.

These patients are kept under close observation, with frequent white-cell and differential counts, and

not be definitely answered at present. It can be answered only after a larger experience over a longer period. At present, it is Dr Bartels's experience that in patients with small thyroid glands who have had the disease for a short time, remissions may be accomplished. How long they will last, no one as yet

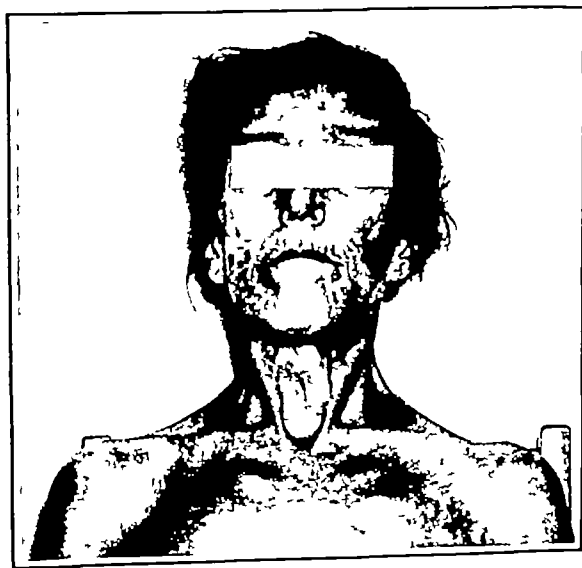


FIGURE 6 *Typical Activated Hyperthyroidism*
This should be compared with Figure 7, which shows typical apathetic hyperthyroidism



FIGURE 7 *Typical Apathetic Hyperthyroidism*
Note the lack of activation and thyroid enlargement and the wrinkled and pigmented skin

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Of these three drugs it appears reasonable to say that, at least so far, propylthiouracil appears to possess less danger of the complications that occur with thiouracil and thiobarbital, but is not free from danger, that these drugs, particularly thiouracil and thiobarbital, unless administered by one familiar with their use, will produce mortality rates as high as, if not higher than, that following expert surgery. In experienced hands, however, they will eliminate multiple-stage procedures and largely abolish the mortality of subtotal thyroidectomy. They will find their greatest usefulness in patients with hyperthyroidism with complicating states, such as diabetes, pregnancy and cardiac decompensation.

on the appearance of any real depression of either the white cells or the granulocytes, the drug is immediately withdrawn.

The final question regarding the employment of these three drugs is, Will it be possible by the use of one of them to eliminate the necessity for operation? Can the metabolism be maintained at a normal level over a long period, so that a persisting remission can be accomplished? This question can-

Apathetic Hyperthyroidism

Because a chronic type of hyperthyroidism of low grade that frequently occurs in older people, to which I gave the name "apathetic hyperthyroidism" some years ago is often overlooked, being different from the typical activated hyperthyroidism shown in Figure 6, I call attention to the existence of this atypical type, illustrated in Figure 7

I gave the name apathetic hyperthyroidism to this condition, not with any idea that it represented any special group but merely to call attention to the fact that there is a type of hyperthyroidism without eye signs, without activation, without marked enlargement of the gland and with only moderate tachycardia but particularly associated with marked weight loss and marked myasthenia over a long period and that because of the lack of these outstanding signs this type of hyperthyroidism is often overlooked. I also called attention to the fact several years ago that this type of hyperthyroidism, which is frequently associated with only moderate elevations in basal metabolic rates, is often approached too confidently by the surgeon because it does not have striking signs of overactivation, the condition is not given the attention and caution warranted by the reactions and fatalities that can occur following surgery in this type of hyperthyroidism

I am sure, as I have repeatedly written that there are many patients with such a low grade of this type of chronic hyperthyroidism, exhibiting such unstriking evidences of disease, who are undiagnosed in many communities. It is in these patients that proper preoperative preparation and subtotal thyroidectomy can achieve some of the most brilliant results in the surgery of hyperthyroidism

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Myasthenia

Over the years, everyone who has dealt with patients afflicted with hyperthyroidism has been

Many years ago Dr Henry S Plummer called attention to the association of quadriceps weakness with this disease and devised a chair-standing test

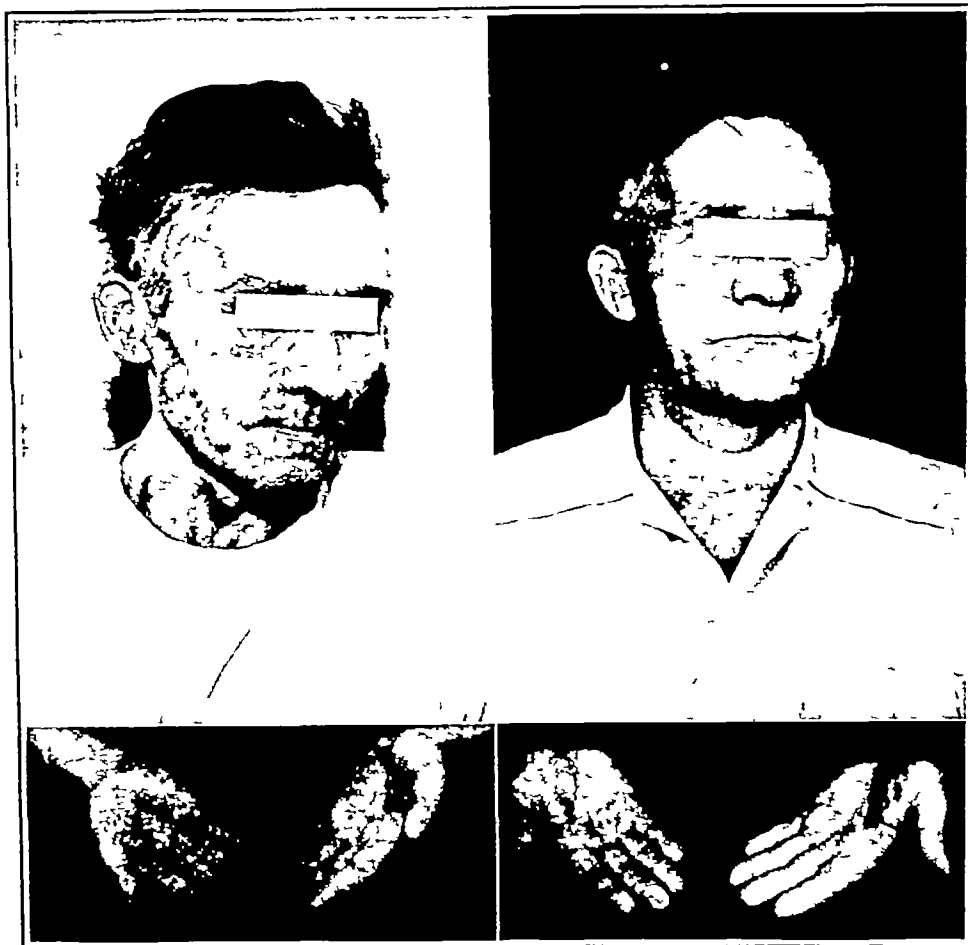


FIGURE 12 Photographs of a Patient with Severe Hyperthyroidism before and after Subtotal Thyroidectomy. Note the effect of severe hyperthyroidism on the muscles of the hands and the improvement following complete relief of hyperthyroidism by operation.

conscious of the frequency with which myasthenia has been associated with the disease and with the

by means of which a patient must step on a chair, thus demonstrating his degree of quadriceps weak-



FIGURE 13 Advanced Intractable Exophthalmos of the Left Eye

The left eye was enucleated, but the right eye was saved by unroofing the bony orbit by the plan shown in subsequent illustrations. Had it been possible to deal with the left eye at the same stage as the right eye in this illustration, both eyes could have been saved by this procedure.

fact that, with relief of the hyperthyroidism, there is complete disappearance of the myasthenia

ness. Several years ago I devised a straight-leg test to demonstrate that, owing to quadriceps weakness,

sents a perfect result, with no return of decompensation, no myxedema, auricular fibrillation or per- failure Again, the name "thyrocardiac" was given to these cases not because they represent an unusual

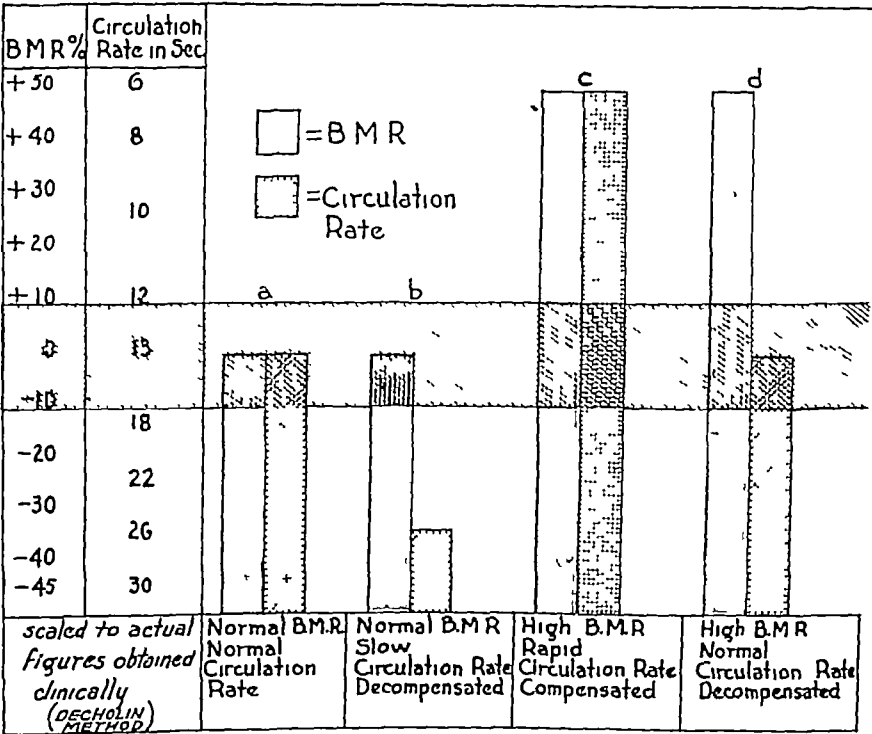


FIGURE 9 The Relation of Circulation Rate to Heart Failure With a normal basal metabolic rate and a slow circulation rate (b) cardiac decompensation results, with a high basal metabolic rate and a high circulation rate (c) there is no failure, with a high basal metabolic rate and a normal circulation rate (d), incapable of being compensatorily elevated, the heart becomes decompensated The last represents the state in the thyrocardiac patient (reproduced from Lahey et al⁴ by permission of the publisher)

sisting hyperthyroidism, Grade II a perfect result so far as no return of cardiac failure is concerned

or extraordinary group but to call attention to the hopefulness of restoring cardiac compensation with

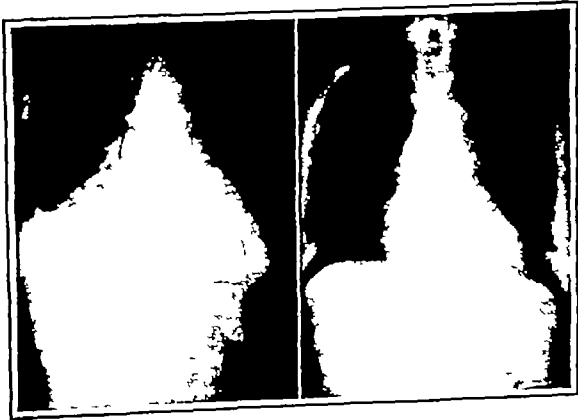


FIGURE 10 Roentgenograms Showing the Change in the Size of the Heart Shadow following Subtotal Thyroidectomy With return of the basal metabolic rate to normal, the circulation rate matches the cardiac capacity and compensation is restored



FIGURE 11 Photomicrograph of a Section of Skeletal Muscle from a Patient with Severe Hyperthyroidism Note the histologic signs of true muscular dystrophy

but with myxedema or persistence of some hyperthyroidism, and Grade III a return of cardiac

a high prospect of permanent maintenance in a group of patients otherwise doomed to death or disability because of the fact that decompensation cannot be restored until the load imposed on the heart by hyperthyroidism is eliminated

muscles and the retro-orbital fat, resulting in edema-ous enlargement of the muscles and infiltration of the retro-ocular fat and thus crowding the eye forward and producing lid pressure on the conjunctiva, with consequent loss of nutrition and with ulceration and infection (Fig 13)

Up to ten years ago, we had seen eyes lost in 6 cases as the result of this condition. Since the employment of the Naffziger operation by the neurosurgeons of the Clinic, Drs Gilbert Horrax and James L. Poppen, no eyes have been lost in patients with intractable exophthalmos.⁶ Because

the periosteum of the orbit. There is a bulging of the retro-orbital fat as soon as the periosteal covering over the orbital canal is opened. Figure 16 illustrates diagrammatically the anatomy of the orbital canal, the segment of orbital plate to be removed, the bulging of ocular muscles and retro-orbital fat through the decompressed, unroofed, orbital cavity and the projection of the eye pre-operatively and its recession following decompression.

Although this operation, devised by Naffziger, will not abolish in many of the cases the unsightly

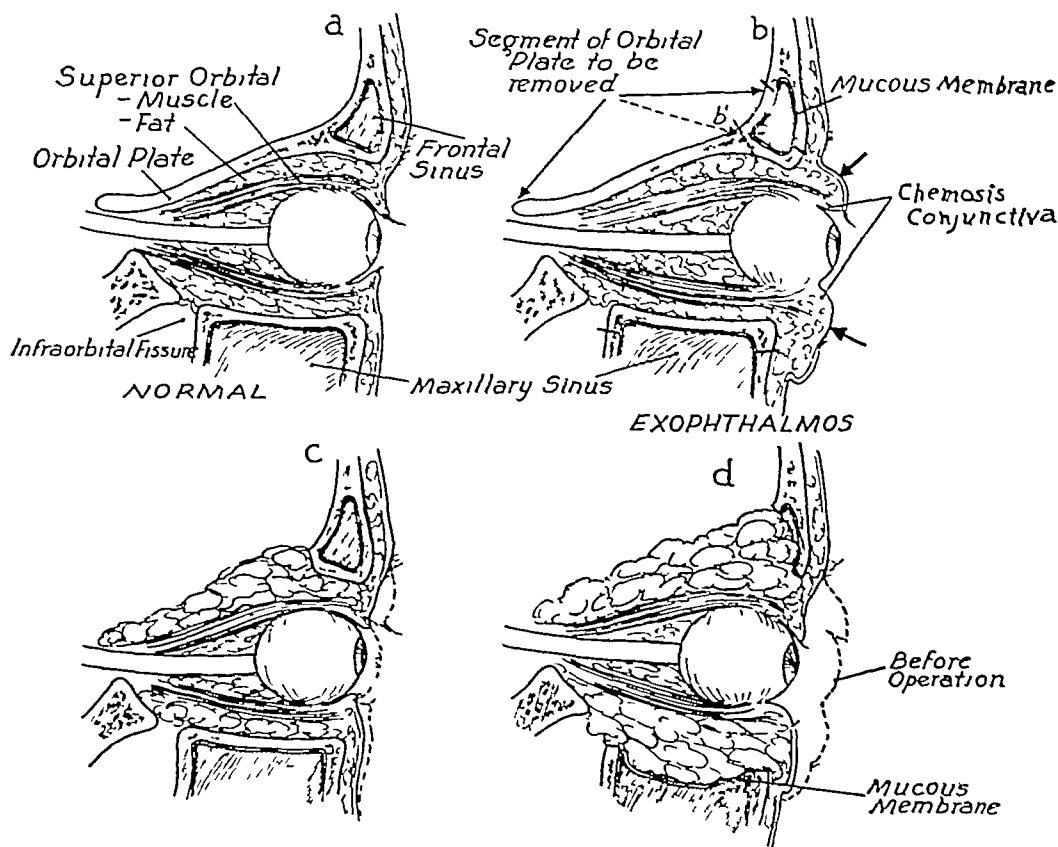


FIGURE 16 Diagrams Representing the Various Steps in Decompression of the Eyeball in Intractable Exophthalmos

of the serious danger to the eyes in patients with extreme exophthalmos I wish particularly to urge that, should there be any evidences of lid pressure, as shown in Figure 14, which illustrates the pre-operative state and postoperative result in such a case, prompt measures should be undertaken by means of orbital decompression to relieve this pressure. Figure 15 demonstrates the method of decompressing the orbital canal. After exposure, the parietal bone flap is turned down, the frontal lobe of the brain is turned up, the bony roof of the orbit is rongeuired away and an incision is made in

exophthalmos, it will, if done in time, prevent ulceration, infection and, if loss of blood supply has not already taken place, save the eye. It will obviously be of no value, however, to patients who are sent for management at the stage shown in the left eye in Figure 13.

Liver Function

In addition to the external results of the advanced stage of hyperthyroidism shown in Figure 1, serious nonvisible and often unappreciated effects are going

a patient with hyperthyroidism, sitting in a chair, could not hold his leg out straight as long as a normal person could

It is of interest to note that Dr Bartels has demonstrated by means of muscle biopsies that this

deals with thyroid disease in large numbers, that many men go through an entire medical lifetime without having to deal with such a case. Because any day such a case may arise in anyone's experience, I wish to present the dangers that occur in

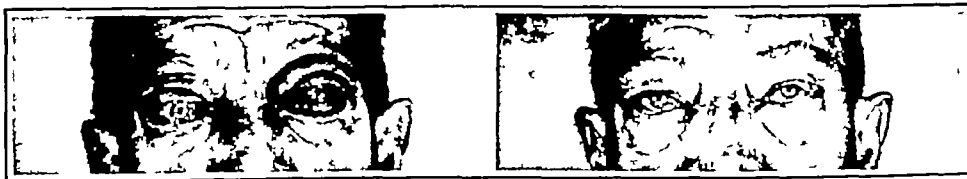


FIGURE 14 Intractable Exophthalmos with Increasing Lid Pressure

The photograph on the right shows the relief from pressure obtained following unroofing of both bony orbital canals (reproduced from Poppen⁶ by permission of the publisher)

is a true muscular dystrophy (Fig 11). Figure 12 illustrates the change in the muscular state of the hands of a patient with hyperthyroidism preoperatively and postoperatively. As stated above, this is one of the real but unappreciated effects of the excessive metabolism in patients with hyperthyroid-

intractable exophthalmos and the measures that may be undertaken to prevent the loss of eyes in these patients.

It is important to remember that intractable exophthalmos is more frequently associated with myxedema, either postoperative, spontaneous or as

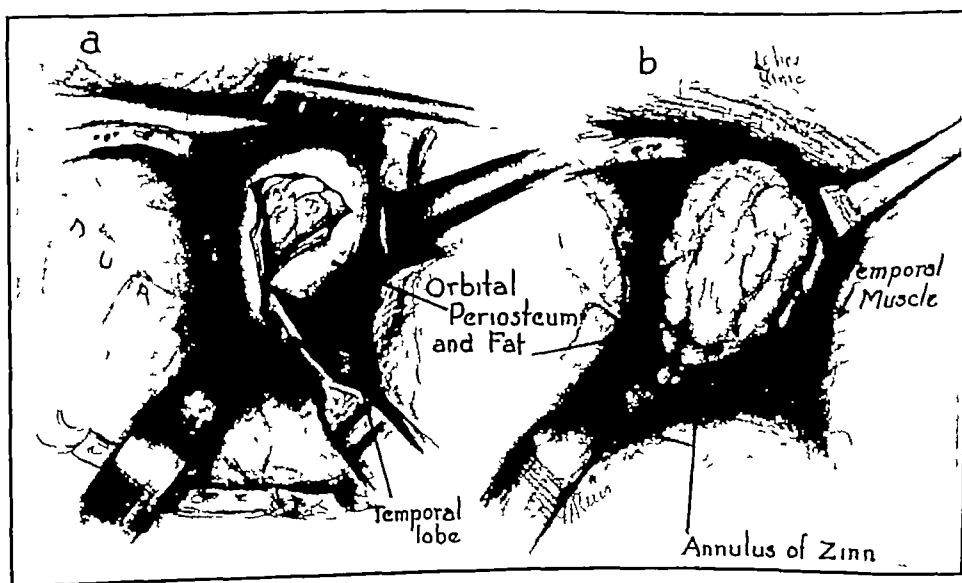


FIGURE 15 Steps in the Operation for Intractable Exophthalmos

In a, through a parietal flap with the frontal lobe elevated, the bony roof of the orbit has been rongeuired away and the incised orbital periosteum and the underlying fat are seen, in b there is upward bulging of retro-ocular fat and muscles, with relief of forward pressure on the eye

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Exophthalmos

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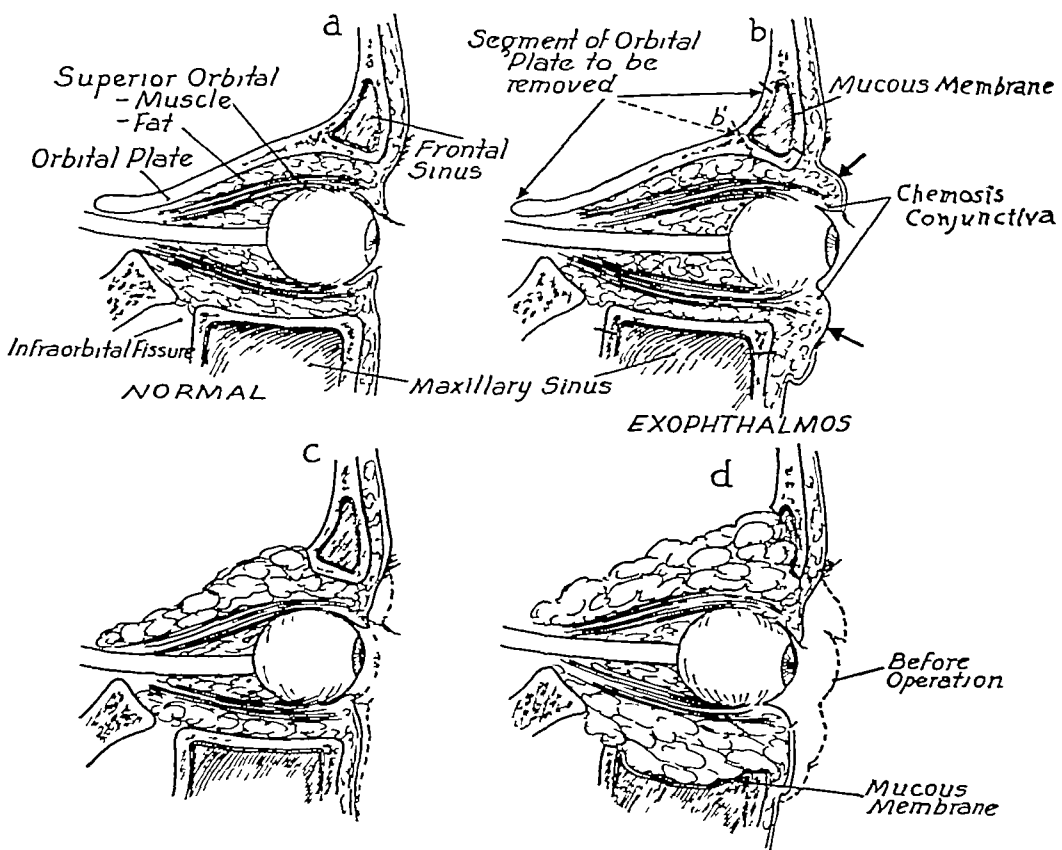


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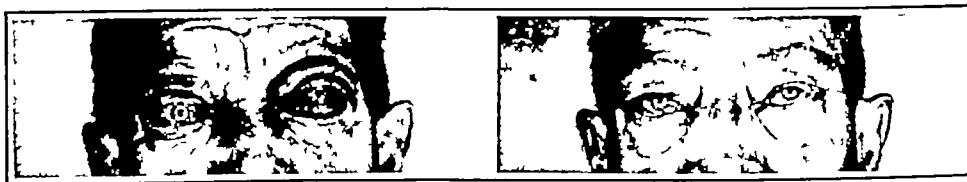


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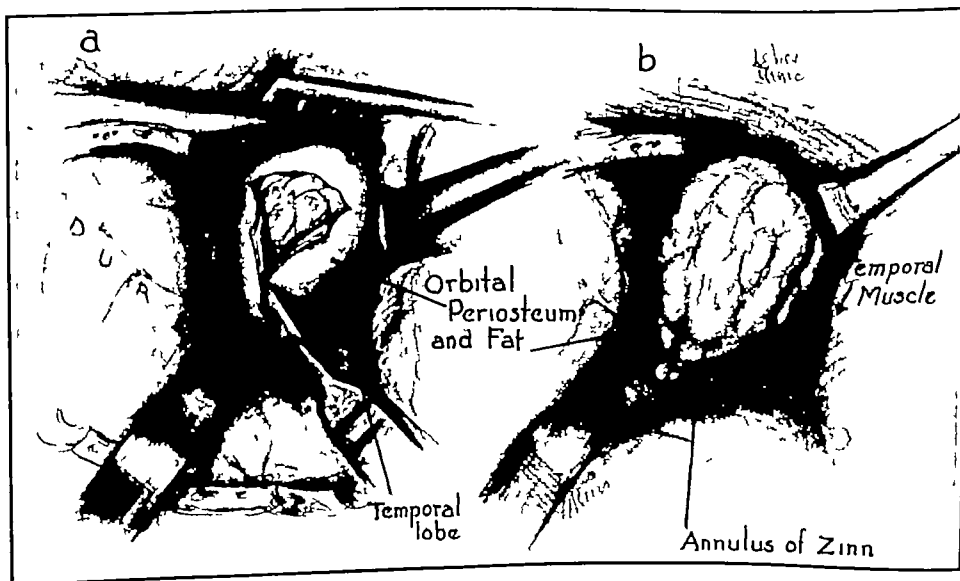


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with sixteen movements daily. It is to be noted, has been our experience and that of many others that following the administration of this material there is prompt control of the diarrhea. Lipocaic is a product of the alpha cells of the pancreas, proposed by Dragstedt,⁹ of Chicago, and

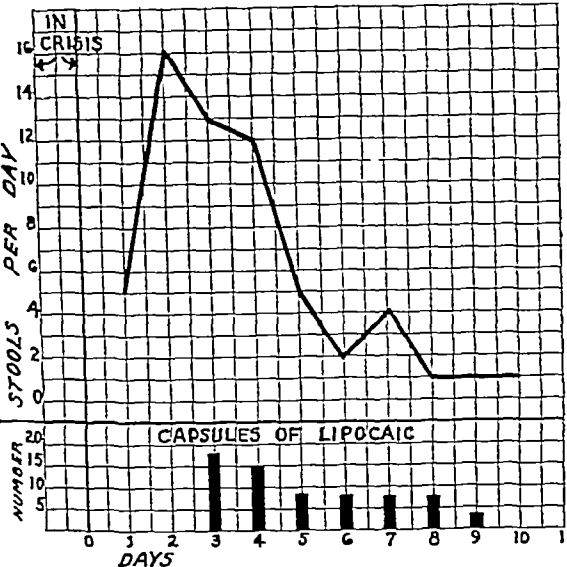


FIGURE 19 The Effect of Lipocaic on the Diarrhea associated with Hyperthyroidism. Note the return to a normal number of bowel movements within a week following the administration of this material (reproduced from Bartels⁸ by permission of the publisher)

has to do with fat metabolism. It has proved to be of great value in controlling the undesirable diarrheas often associated with thyroid crises, which make it



FIGURE 20 Photograph of a Specimen Showing the Origin of a Carcinoma within an Adenoma of the Thyroid Gland. Note the complete erosion of the capsule between the two arrows where the centrally originating carcinoma has extended to involve the parenchyma (reproduced from Lahey, Hare, and Warren¹⁰ by permission of the publisher)

impossible to manage these patients so long as such a large fluid and fuel loss continues

Cancer of the Thyroid

Cancer of the thyroid used to be considered a particularly depressing aspect of thyroid disease. This was largely because patients with this lesion were often not seen until extensive malignant processes involved the entire neck, with large, nodular and fixed masses.

To approach this subject from the proper point of view, it should be realized that practically all

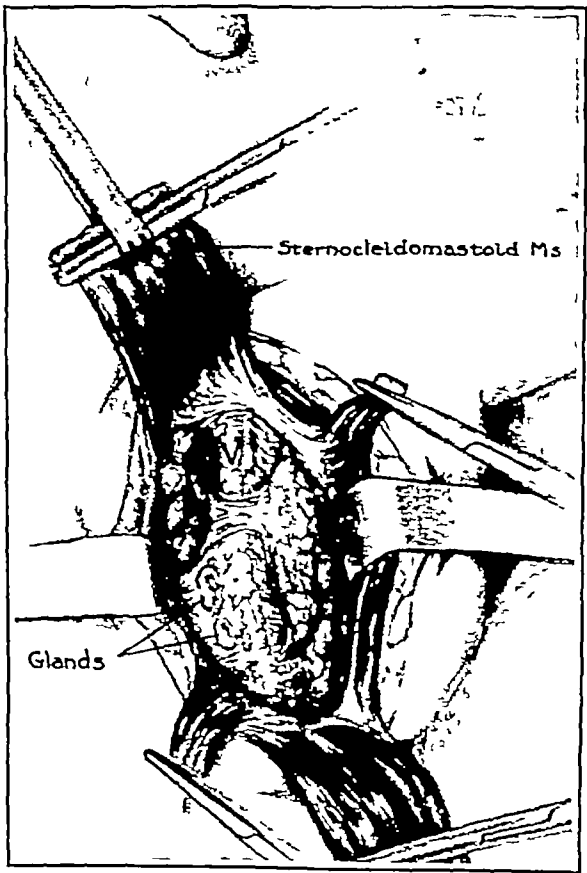


FIGURE 21 A Drawing of Typical Lateral Aberrant Thyroid Masses

Note their glandlike structure and their location running up and down laterally to the internal jugular vein

thyroid cancers originate from two sources — fetal or embryonal adenomas (Fig 20) and aberrant thyroid glands (Fig 21). For practical purposes, nearly all thyroid cancer originates in a previously existing benign, true adenoma of the gland, the percentage of malignancy being greater in fetal or embryonal adenomas than in the true, fully differentiated adenomas. Figure 20 shows a cancer arising within the capsule of a thyroid adenoma, with invasion and destruction of the capsule. Graham,^{11, 12} a number of years ago, demonstrated that so long as the cancer is within the fibrous capsule of the adenoma there will be but rare metastases to lymph

on at the same time, among which depression of liver function pre-eminently causes death

Figure 17 illustrates the effect, as determined by Bartels,⁷ on the glycogenic function of the liver as demonstrated by hippuric acid excretion in relation

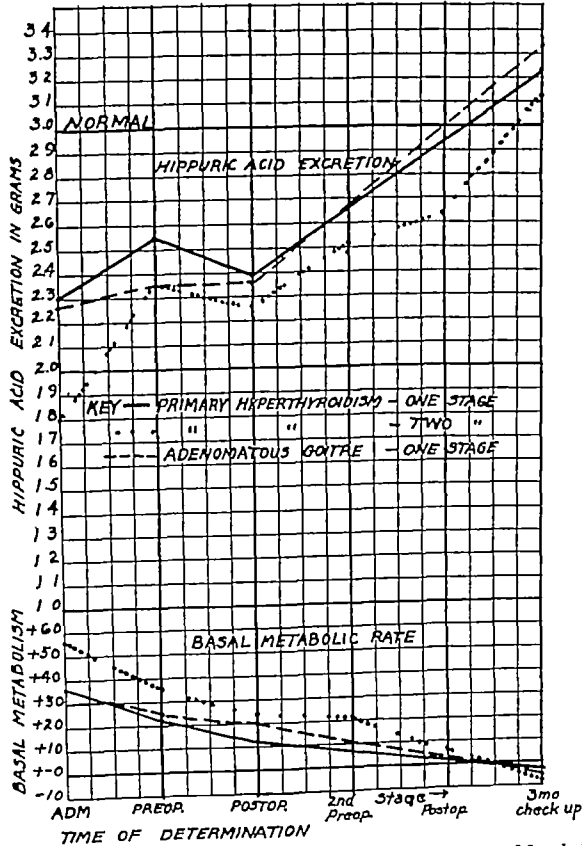


FIGURE 17 Hippuric Acid Excretion and Basal Metabolic Rate in Hyperthyroidism

This chart shows the effect on liver function, as determined by hippuric acid excretion, in patients with three types of hyperthyroidism. Note the relation of the depression of hippuric acid excretion to the elevation of the basal metabolic rate, and the return of both to normal following operation (reproduced from Bartels⁷ by permission of the publisher)

to the severity of the disease in the three groups and grades of hyperthyroidism, as well as the return of the glycogenic function to normal with the return of the metabolic rate to normal. It is to be noted that the degree of depression of this glycogenic function of the liver is quite accurately related to the depression of the metabolism and to the return to normal of the basal metabolic rate following subtotal thyroidectomy.

Figure 18 shows the correlated effects on serum albumin and total serum protein preoperatively and postoperatively following the restoration of the basal metabolic rate to a normal level in patients with hyperthyroidism.

It is of value to present these graphic illustrations of the unseen effects of hyperthyroidism on patients

who are permitted to maintain high basal metabolic rates over long periods, because of their relation to mortality. I have often observed in the past years, after having seen many patients die of hyperthyroidism before any operation could be performed, that thyroid deaths, associated with hyperthermia and jaundice, were more frequently the result of diminished liver function than that of the excessive metabolism on any other single structure in the body.

Lipocaic in the Diarrhea of Hyperthyroidism

Owing to the fact, as stated above, that family physicians and patients are less fearful of surgical

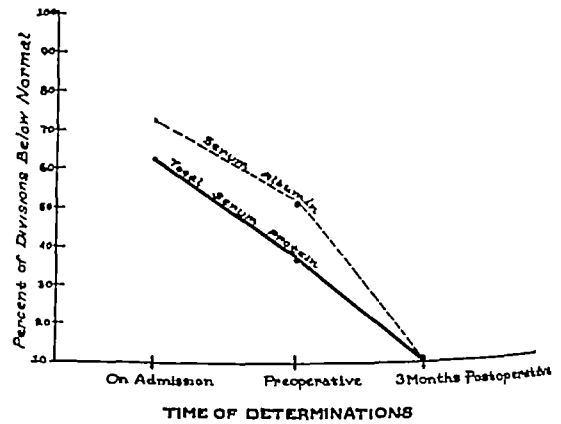


FIGURE 18 Percentage of Serum Albumin and Total Protein Levels below Normal before and after Operation. This chart demonstrates the effect of hyperthyroidism on the proteogenic function of the liver.

procedures for hyperthyroidism than they were in past years, few patients now present themselves to us for care in a state of thyroid crisis. Occasional patients, however, are still sent to the Clinic for management in a state of crisis, and among the conditions making these states most difficult to deal with is that of the diarrhea associated with hyperthyroidism. Bartels,⁸ who has been interested

TABLE 4 Possible Causes of Diarrhea in Hyperthyroidism

HYPERMOTILITY	
Direct action of thyroid secretion on the intestinal musculature	
Vagal stimulation by thyroid excretion	
Reduction in gastric acids	
Retarded intestinal absorption (primary or secondary)	
Altered pancreatic secretion	
Reduced hepatic function	
Altered adrenal function	

in this subject, has listed the possible causes of diarrhea in hyperthyroidism, one of the most probable of which is altered pancreatic secretion, which is known to exist in severe states of hyperthyroidism (Table 4).

Figure 19 demonstrates the effects of the administration of lipocaic to such a patient in crisis,

with sixteen movements daily. It is to be noted that this has been our experience and that of many others following the administration of this material. There is prompt control of the diarrhea. Lipocaic is a product of the alpha cells of the pancreas, proposed by Dragstedt,⁹ of Chicago, and

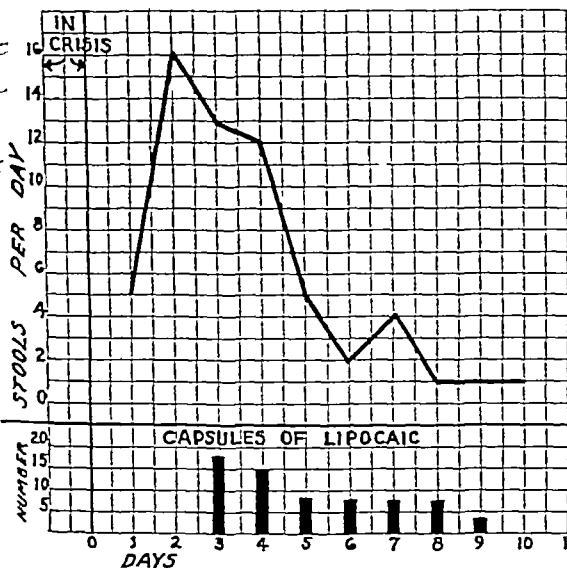


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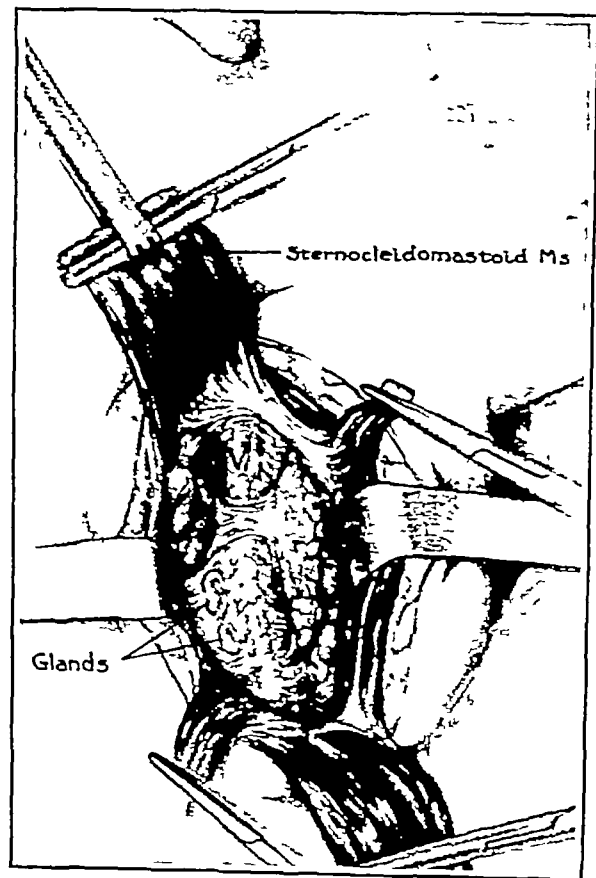


FIGURE 21 A Drawing of Typical Lateral Aberrant Thyroid Masses

Note their glandlike structure and their location running up and down laterally to the internal jugular vein

thyroid cancers originate from two sources — fetal or embryonal adenomas (Fig 20) and aberrant thyroid glands (Fig 21). For practical purposes, nearly all thyroid cancer originates in a previously existing benign, true adenoma of the gland, the percentage of malignancy being greater in fetal or embryonal adenomas than in the true fully differentiated adenomas. Figure 20 shows a cancer arising within the capsule of a thyroid adenoma, with invasion and destruction of the capsule. Graham,^{11, 12} a number of years ago, demonstrated that so long as the cancer is within the fibrous capsule of the adenoma there will be but rare metastases to lymph

nodes, such metastases as occur being of blood-borne variety, but that as soon as the growth has eroded the capsule and involved the true parenchyma of the thyroid gland, with its rich supply of lymphatics, early lymph-node metastases will ensue. This illustration is presented to re-emphasize that the best approach to the treatment of cancer of the thyroid gland — in spite of the fact that the incidence of malignant degeneration within these

Dr Ficarra and I¹³ reported the experience in the Clinic with 47 patients with lateral aberrant thyroid glands in which the tissue on removal showed papillary adenocarcinoma so frequently that I strongly believe that all lateral aberrant thyroid glands should be considered potentially cancerous.

Table 5 demonstrates that this type of cancer is of a relatively low grade since but two of the patients died of carcinoma. It is to be noted, however, that

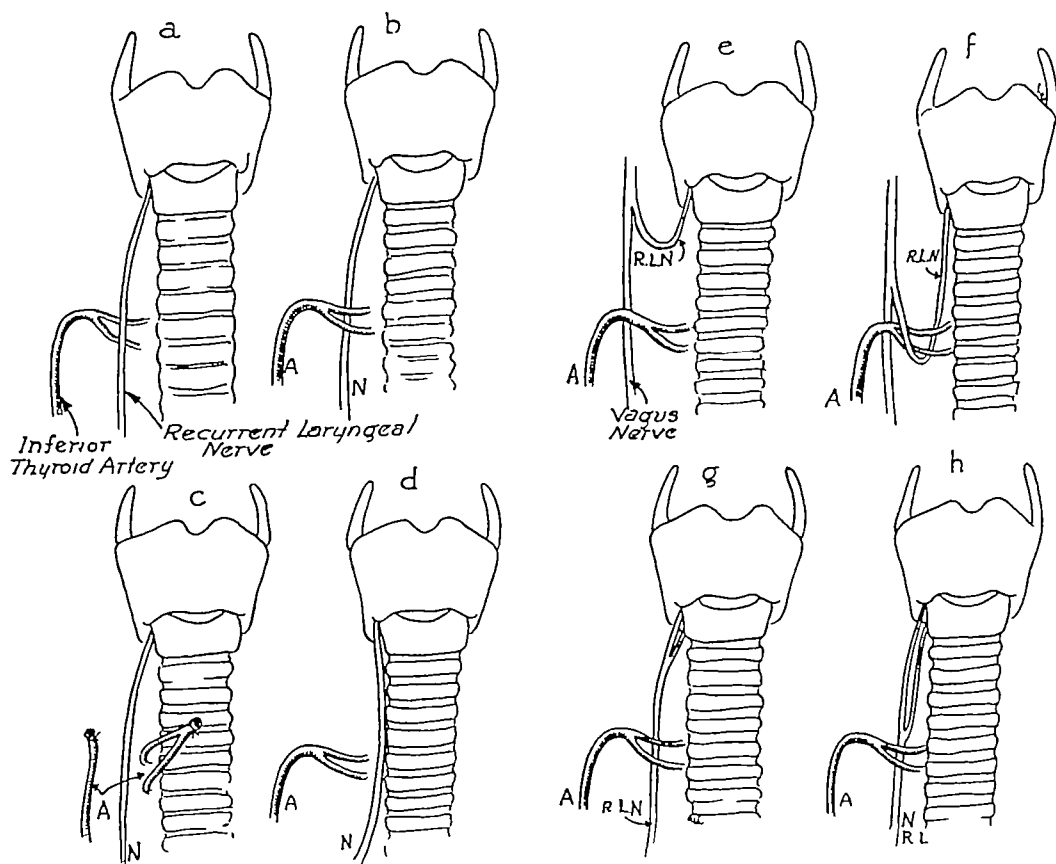


FIGURE 22 The Various Normal and Abnormal Positions of the Recurrent Laryngeal Nerve (reproduced from Lahey¹³ by permission of the publisher)

adenomas is relatively small, perhaps not over 5 per cent — is to remove all discrete adenomas before they have become malignant or if they have become malignant, before the capsule of the adenoma has been eroded. Although a change in consistence, such as increasing firmness or increasing fixation, is an indication of possible malignant degeneration within these adenomas, I am convinced that all discrete adenomas, since their removal is not associated with any mortality, should be removed as soon as they are discovered and before malignant degeneration has taken place.

Figure 21 presents an example of lateral aberrant thyroid glands. In a recent article on this subject,

6 patients had recurrences, required reoperation and are well and that 3 are living with recurrences, one of whom has pulmonary metastases.

Lateral aberrant thyroid glands, originating as they do in the ultimobranchial bodies from the fourth pharyngeal pouch, are located as lateral glandlike tumors running up and down in front of and in relation to the sternomastoid muscle and internal jugular vein (Fig 21). They may be multiple glandlike structures or a single large tumor mass. They should, in our opinion, all be removed radically, and when on pathological section they prove to be papillary adenocarcinomas, they should be treated radically by block dissection of the neck,

consisting of removal of the entire internal jugular vein from the mastoid to the clavicle, together with the entire front half of the sternomastoid muscle, all the adjacent lymph nodes and all the thyroid lobe on that side

It is important in these cases to remove the thyroid lobe on the same side when papillary adenocarcinoma occurs in lateral aberrant glands because of the possibility of division between the aberrant gland originating in the

the artery by severing the artery (c), and its fusion with the trachea in intrathoracic goiter from being pressed against the trachea (d) The recurrent laryngeal nerve often does not descend into the larynx but crosses from the vagus directly into the larynx (e) or descends as far as the inferior thyroid and then ascends to enter the larynx (f) There are two different types of extralaryngeal division of the recurrent laryngeal nerve into its adductor and abductor fibers (g and h)

It has been taught to every surgeon in the Clinic that exposure of the recurrent laryngeal nerve, which is not difficult, not only adds to the preservation of the vocal-cord innervation by avoiding injury

TABLE 5 Data in 47 Cases with Lateral Aberrant Thyroid Glands

CONDITION OF PATIENT	CASES BEFORE 1939	CASES SINCE 1939
No recurrence	20	13
Cooperation for recurrence patient well	5	1
Patient living with recurrence	3*	0
Death from recurrent cancer	2	0
Operation too recent for evaluation	0	3
Total	30	17

*One patient has pulmonary metastases

ultimobranchial bodies with the true gland often results in the inclusion of malignant degeneration within the associated lobe of the thyroid gland itself This probably explains why in these cases papilliferous aberrant thyroid nodules similar to those lateral to the thyroid gland are occasionally found within the substance of the thyroid gland

Table 6 presents a five-year follow-up study of 231 patients with cancer of the thyroid gland, in-

TABLE 6 Five-Year Survival in 231 Cases of Carcinoma of the Thyroid Gland

TYPE OF CARCINOMA	SURVIVAL %
Adenoma with blood-vessel invasion	71
Papillary cystadenoma malignant	62
Papillary adenocarcinoma	80
Alveolar adenocarcinoma	27
Small-cell carcinoma	22
Giant-cell carcinoma	17
Fibrosarcoma	33

cluding the different types of malignancy, with their five-year survival rates¹ As will be seen from these figures, which represent the treatment of thyroid cancer by radical removal followed by intensive irradiation, this condition is by no means as hopeless as it was formerly thought to be

Recurrent-Nerve Paralysis and Preservation of Parathyroid Glands

Some years ago I¹⁴ suggested that the recurrent laryngeal nerve be dissected and demonstrated in every patient operated on for thyroid disease Figure 22 demonstrates the usual and the unusual positions of the recurrent laryngeal nerve It shows the relation of the nerve to the inferior thyroid artery, either before or behind it (a and b), the methods of exposing the nerve when it is behind



FIGURE 23 Roentgenogram of a Large Intrathoracic Goiter Obviously, this intrathoracic mass could not have been made to pass through the upper thoracic strait It is in this type of intrathoracic goiter that breaking down the center of the goiter to collapse it makes it possible to deliver the mass without removing a portion of the chest wall or the clavicle

to the nerve but also, because the complete anatomy of the thyroid gland is exposed, permits more radical removal of thyroid tissue, since one knows where the nerve and the parathyroid glands are and can thus avoid leaving behind large sections of the gland to protect these structures, as when the nerves are not demonstrated and visualized

The technical step of demonstration of the inferior thyroid artery and the recurrent laryngeal nerve has in addition made it possible to find in

practically every patient operated on for thyroid disease in the Clinic at least two parathyroid glands. It is now our belief that practically no thyroid operation should be done in which it cannot be demonstrated that two parathyroid glands with a good blood supply have been preserved, thus avoiding the possibility of one of the most undesirable com-

with thyroid operations to dissect and expose even recurrent laryngeal nerve in every patient operated on in the Clinic for thyroid disease, to be certain that the nerves are preserved.

Intrathoracic Goiter

Figure 23 illustrates a typical, large, intrathoracic goiter. Figure 24 shows the specimen of such an intrathoracic goiter after removal, and Figure 25 the deviation of the trachea in such an intrathoracic goiter. Figure 26 demonstrates the compression effect on the trachea, resulting in diminution in caliber to a half in such an intrathoracic goiter. In Figure 27 is shown an infrared photograph of a patient before the removal of a large intrathoracic goiter to demonstrate the effect on compensatory



FIGURE 24 Photograph of a Large Extrathoracic and Intrathoracic Goiter

The small portion above is the extrathoracic goiter, and the large mass below the intrathoracic goiter (see Fig. 23)



FIGURE 25 The Effect on the Trachea of a Large Intrathoracic Goiter

Note the marked forward deviation of the trachea

plications that occasionally occur with subtotal thyroidectomy for hyperthyroidism—that is, tetany.

Paralysis of the recurrent laryngeal nerve is not serious when but one nerve is injured, since the vocal cords on the uninjured side will overcompensate to provide a reasonably good voice, and there will usually remain a reasonably adequate glottic space for breathing. When, however, both recurrent laryngeal nerves are injured, eventual fibrosis of the vocal cords, together with arytenoid fixation, results in such a narrowing of the glottic space that there is an inadequate airway for the intake of a sufficient amount of oxygen to meet the demands of only moderate physical activity. It has, therefore, proved worth while in this large experience

venous circulation in the superficial thoracic veins brought about by the pressure of an intrathoracic goiter on the internal jugular veins, interfering with the return venous flow from the head. One should note the enormous dilatation of the superficial thoracic veins as compared with the normal superficial thoracic venous circulation.

When one considers the diameter of such an intrathoracic goiter, it becomes obvious that such an intrathoracic tumor cannot be made to pass through the upper thoracic strait because its diameter is so much greater than that of the strait. It is in such

es that I wish particularly to call attention to the fact that it is not necessary to remove ribs or to divide the clavicle in an attempt to enlarge the upper thoracic aperture so that an intrathoracic tumor of this diameter can be made to pass through it. By ligating the superior and inferior thyroid arteries, together with the venous connections of the thyroid to the internal jugular vein, it is possible completely to devascularize this intrathoracic tumor, and to make an incision into the capsule, insert a finger

before an attempt is made to remove such an intrathoracic goiter from the chest, to introduce a rigid-walled, flexible intratracheal tube into the trachea under direct laryngoscopy so that the manipulations necessary for the removal of such an intrathoracic goiter do not result in compression of the trachea and produce such interference with respiration and anesthesia that they cannot be maintained.

A great many patients have been operated on in the Clinic with completely intrathoracic goiters



FIGURE 26 *The Compression Effect on the Trachea of a Large Intrathoracic Goiter*
Note the reduction of the caliber of the trachea to one half to one third its normal size

into the center of the semisoft mass, break its center down, suck out its semiliquid contents, separate its capsule from the surrounding pleura and gradually deliver the entire tumor through the upper thoracic strait without enlarging that aperture.

In Figure 26, in which the caliber of the trachea has been reduced to approximately one third the normal size by the pressure of the intrathoracic goiter, it can be demonstrated how necessary it is

large enough to require extensive manipulative measures within the thorax in which the compression of the trachea has been of such extent that an intratracheal tube could not be introduced under a general anesthesia, such an anesthesia would have resulted in choking from closing of the small remaining tracheal airway. In such cases it has been possible for our anesthetists to introduce the intratracheal

tube first into the cocainized larynx and then to induce general anesthesia safely

It is to be noted that the effect of an intrathoracic goiter is not only one of pressure on the trachea to interfere with breathing but also one of pressure on

a previously obvious thyroid tumor in the neck but disappeared one should seriously consider the possibility that it has descended into the superior mediastinum, that an adenomatous goiter whose lower pole cannot be felt should seriously be considered to have become intrathoracic, and that in any patient with a large intrathoracic goiter disappearing beneath the clavicle, x-ray films should be taken particularly directed toward demonstrating the trachea to determine whether or not there is deviation of the trachea by an intrathoracic goiter and an extension of the goiter into the mediastinum.

Finally, all adenomatous enlargements of the thyroid gland that tend to extend beneath the clavicle should be removed before they become intrathoracic goiters of such magnitude as those illustrated in Figures 23, 24 and 25

* * *

This paper represents a review of thirty years' experience with the surgery of the thyroid gland. In it are discussed some of the newer developments and some of the less frequent complications of thyroid disease as seen in a clinic dealing with these states in large numbers of cases

REFERENCES

1. Lahey F H, Bartels E C, Warren S, and Meissner, W A. Thiouracil — its use in preoperative treatment of severe hyperthyroidism. *Surg, Gynec & Obst* 81 425-439 1945
2. Bartels E C. Use of thiouracil in preoperative preparation of patients with severe hyperthyroidism. *Ann Int Med* 22:365-372, 1945
3. Hamilton B E and Lahey F H. Thyrocardias: their diagnosis, difficulties, their surgical treatment. *Surg, Gynec & Obst* 38 10-14 1924
4. Lahey F H, Hurxthal, L M and Driscoll R E. Thyrocardia: disease review of 614 cases. *Ann Surg* 118 681-693, 1943
5. Naffziger H C. Progressive exophthalmos following thyroidectomy: its pathology and treatment. *Ann Surg* 94 582-586 1931
6. Poppen J L. Exophthalmos: diagnosis and surgical treatment of intractable cases. *Am J Surg* 64 64-79, 1944
7. Bartels E C. Liver function in hyperthyroidism as determined by hippuric acid test. *Ann Int Med* 12 652-674, 1938
8. *Idem*. Lipocain in treatment of diarrhea of hyperthyroidism preliminary report. *West J Surg* 49 439-446 1941
9. Dragstedt L R. Present status of lipocain. *J A M A* 114 78-81, 1940
10. Lahey F H, Hare, H F and Warren S. Carcinoma of thyroid. *Ann Surg* 112 977-1005 1940
11. Graham, A. Malignant epithelial tumors of thyroid. *Surg, Gynec & Obst* 39 781-790 1924
12. *Idem*. Malignant tumors of thyroid — epithelial types. *Ann Surg* 82 30-44 1925
13. Lahey F H, and Ficarra B J. Lateral aberrant thyroid. *Surg, Gynec & Obst* 82 705-711 1946
14. Lahey F H. Routine dissection and demonstration of recurrent laryngeal nerve in subtotal thyroidectomy. *Surg, Gynec & Obst* 66 775-777 1938
15. *Idem*. Exposure of recurrent laryngeal nerves in thyroid operations: further experiences. *Surg, Gynec & Obst* 78 239-244 1944

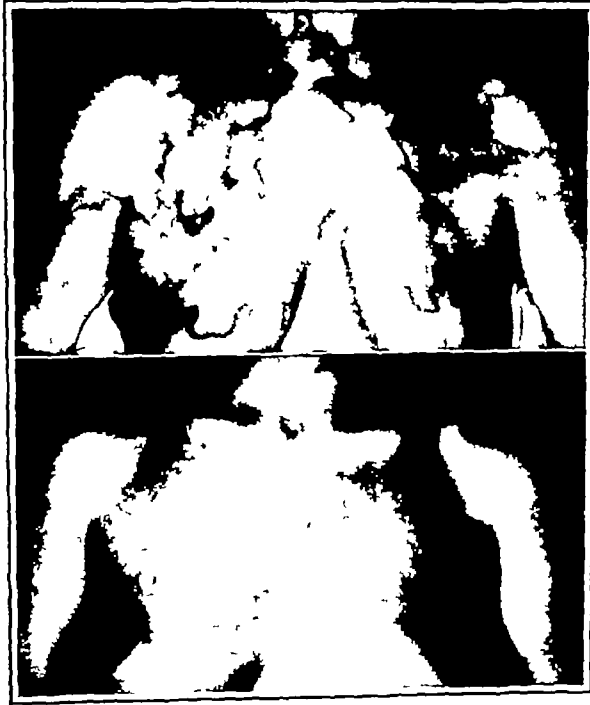


FIGURE 27 Infrared Photographs of a Patient with an Intrathoracic Goiter before and after Removal

Note the enormous compensatory dilatation of the superficial thoracic veins previous to the removal of the intrathoracic goiter (upper photograph) as compared with normal superficial thoracic venous circulation after operation (lower photograph)

the internal jugular veins, increasing intracranial venous pressure and interfering with the return of venous flow from the head and neck

Before leaving this subject I wish particularly to call attention to the fact that in any patient in whom

CLINICAL NOTES

VISCERAL LEISHMANIASIS*

REPORT OF A CASE

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VISCERAL leishmaniasis (kala-azar) in American personnel returning to the United States has been rare. Burchenal and Woods§ reported 3 cases in American troops who had contracted the disease in the Mediterranean area. It is estimated that approximately 60 cases of the disease have occurred in American troops during World War II, the majority of which were contracted in the India-Burma Theater. The endemic areas where American personnel have been stationed are India, North Africa, Sicily, Southern Italy, Manchuria and China.

Visceral leishmaniasis is an infective disease that is characterized by fever, splenomegaly and usually hepatomegaly, as well as by a loss of weight and leukopenia, generally running a chronic course. Since the incubation period varies from six days to six months and since the course of the disease may last a year and a half, the total time from the inception to the termination of the disease is approximately two years. This is definitely of importance, since the soldier may have time to become a civilian and manifest the symptoms of the disease long after his return to the United States.

It is believed that this disease is worthy of attention because, if untreated, it is fatal in 90 per cent of cases, whereas prompt diagnosis and treatment ensure recovery in approximately 95 per cent.

K. P., a 22-year-old veteran, was admitted to the hospital on February 8, 1946, complaining of chills, fever and a mild headache. The patient had been stationed in and around Calcutta, India, for 2 years and had returned to the United States in December, 1945. He had not been on suppressive quinacrine (Atabrine) therapy and had not had malaria. There was nothing of significance in the family history, all members of the immediate family being well. The patient himself had been well until the onset of the present illness, which had begun during the 3rd week in December, while he was en route home from India. He noticed at first a chilliness followed by a slight fever every evening. He stated that he had reported to the sick bay, where he was treated for an upper respiratory infection. After arrival in the United States he was discharged from the Army, apparently, little or no evidence of the illness was present at that time, and the final Army physical examination was negative. The patient stated that the symptoms increased somewhat in severity on about January 1, but that he still did not feel

sick enough to consult a physician. In the middle of January, however, at his mother's insistence, he consulted a physician. The patient was placed on bed rest and given a high-calorie diet and some medication, which he believed to be a "tonic." All symptoms gradually subsided, and the patient felt well enough to make a trip away from home. Early in February, however, there was an exacerbation of symptoms, and actual chills, with high temperatures, occurred. Occasional mild headaches were also noted. The patient stated that he had lost about 15 pounds since the onset of the illness.

Physical examination revealed a poorly developed and poorly nourished man, who did not appear acutely ill. The temperature was 104°F, the pulse 126, and the respirations 24. The blood pressure was 110/75. The head was of normal configuration. The scalp, ears, eyes and nose were normal. There was a fine tremor of the tongue. The pharynx was not injected. There was no cervical adenopathy and no stiffness or other abnormality of the neck. The thyroid gland was not palpable. The chest was symmetrical, with prominent costochondral junctions. Tactile fremitus, resonance and breath sounds were normal throughout. There were no rales or adventitious sounds. The heart borders were within normal limits, there were no murmurs. The abdomen was flat, with no tenderness. The spleen was palpable 3 cm. below the costal margin, but the liver was not palpable. The extremities showed no limitation of motion, but all limbs had a fine tremor on motion. The axillary lymph nodes were not palpable, and the inguinal lymph nodes were not enlarged. The skin was clear, except for a suggestion of pigmentation along the lateral inferior orbital aspects. The reflexes were normal throughout.

Examination of the blood revealed a red-cell count of 4,630,000, with a hemoglobin of 90 per cent and a white-cell count of 5500. During the next 18 days the red-cell count gradually fell to 2,640,000, the hemoglobin to 52 per cent and the white-cell count to 3750. The differential count showing a marked shift to the left. During the same period the sedimentation rate rose from 8 to 29 mm. per hour. Repeated smears for malarial parasites were negative, as were blood serologic studies. Agglutination tests for the organisms of typhoid, paratyphoid, typhus and undulant fever were negative. Roentgenograms of the chest were normal. Urinalyses were negative. The total blood protein was 8.4 gm. per 100 cc., with 4.8 gm. of albumin and 3.6 gm. of globulin. The thymol-turbidity test was 19 units, the cephalin-flocculation test was + + + +, and the icterus index was 8.2. Blood smears and blood cultures (some on NNN mediums) were negative. Marrow smears and cultures were negative for organisms. Gross and microscopic study of the axillary lymph nodes revealed no pathologic changes. Formol-gel tests showed solidification and opacity at the end of 3 hours. Smears from a splenic puncture performed on March 8 revealed typical Leishman-Donovan bodies within endothelial leukocytes. The antimony serum test (performed after the patient had received 0.6 gm. of Neostibosan) was negative.

Although malarial parasites could not be demonstrated, the clinical course resembled that of malaria, and the patient was therefore given a therapeutic trial of quinacrine. The skin became markedly yellow, but there was no improvement. After 10 days of hospitalization the patient was given 240,000 units of penicillin daily for 3 days, but there was no alleviation of symptoms. By that time the spleen was palpated 7 cm. below the costal margin. The liver became palpable, and a small group of lymph nodes in the left axilla became palpable. The patient lost 4 pounds in weight despite a fair appetite and a high-calorie diet. The temperature continued to show a septic rise, varying between 102 and 104°F. Day and night 4-hour temperature readings were started, and it was noted that frequently there was a second elevation during the 24-hour period. A transfusion of 500 cc. of whole blood was given during the last week of February, and another was given during the 1st week in March.

When the diagnosis of visceral leishmaniasis was confirmed by demonstration of the organisms in the splenic pulp, specific antimony therapy was instituted. A total of 4.2 gm. of Neostibosan in fifteen divided doses was given intravenously over a period of 15 days. Within 48 hours the temperature was reduced to nearly normal limits, the appetite improved remarkably, and the profuse perspiration stopped. The spleen in the area of the puncture remained

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†Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

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¶Burchenal, J. H. and Woods, R. P. Visceral leishmaniasis: report of three cases of its occurrence in members of armed forces of United States. *War Med.* 7: 173-177, 1945.

tender During the following 2 days the splenic tenderness increased, with a concomitant increase in the temperature, which at one time reached 102°F. This splenic tenderness was believed to be caused by a small, traumatic, subcapsular hemorrhage. Within 2 days the perisplenitis decreased slowly until the pain entirely disappeared within a month. The spleen decreased slowly in size but remained palpable at the end of 1 month of treatment. The pigmentation around the eyes was no longer detected at that time. On March 27 examination of the blood revealed a red-cell count of 4,160,000, with a hemoglobin of 80 per cent, and a white-cell count of 9000, the sedimentation rate was 20 mm per hour. The gain in appetite, weight and strength was steady, and the patient was discharged from the hospital on April 13.

A case of visceral leishmaniasis (kala-azar) is reported.

The possibility of visceral leishmaniasis should be considered in patients with fever of undetermined origin, leukopenia and splenomegaly who have resided in an endemic area.

CO-EXISTENT PRIMARY CARCINOMA OF THE FALLOPIAN TUBE AND OF THE BREAST

REPORT OF A CASE

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THE purpose of this paper is to discuss primary carcinoma of the fallopian tube, and to submit a report of the first case at the Worcester City Hospital of carcinoma of the fallopian tube and carcinoma of the breast in the same patient. As in the vast majority of cases reported in the literature, the diagnosis of tubal carcinoma was not made preoperatively. It was only suspected during the operation for another pelvic disorder and was confirmed by routine pathological study of the tissues removed during the operation.

Since Rokitsky's original pathological description in 1861 and the first accredited case report presented by Orthmann in 1886, only 449 cases of primary carcinoma of the fallopian tube have been reported in the literature, according to a recent review by Mitchell and Mohler¹. From figures presented by various clinics these authors estimate that the incidence of the disease among genital-tract tumors is 0.5 per cent, secondary carcinoma of the fallopian tube being about ten times more frequent. The extreme difficulty in diagnosis without pathological studies of the diseased tubes has been discussed by many authors, and it is only with this fact in mind that Martzloff,² allowing for unreported as well as unrecognized cases, estimates the upper limit of incidence of primary tubal cancer to be about 0.5 per cent.

The importance of a serous or serosanguineous discharge from the cervix as a diagnostic aid in this disease has been emphasized by numerous authors.^{2,3} Martzloff² states that if recent gestation and disease of the vagina and uterine cavity—especially incipient ulcerating cancer complicated by cervical stenosis—can be excluded, a copious, serosanguineous uterine discharge becomes suspiciously pathognomonic and can be ascribed to an extrauterine origin, logically tubal, and a malignant complication. The symptom complex of an otherwise unexplained intermittent, cramplike, abdominal discomfort relieved by the passage of a watery discharge from the vagina, especially when blood tinged, has been considered to be of diagnostic value by several authors, including Martzloff² and Mitchell and Mohler¹. A further adjunct in diagnosis lies in hystero-graphy, whose value and advisability have been debated by different authors.

The treatment of primary tubal carcinoma consists in surgery, with or without postoperative radium or x-ray therapy. Although Martzloff² considered bilateral salpingo-oophorectomy and pan-hysterectomy the operation of choice and believed that there was no evidence that radium and irradiation were of value, other authors have taken exception to his opinions. Keith⁴ proposed the surgical removal of both tubes and ovaries and all pathologic tissue except the uterus, which is left in situ as a receptacle for radium. He believed that good surgery, in addition to the immediate postoperative use of radium implantation and irradiation, would save a larger percentage of patients than either surgery or x-ray therapy alone.

J. H. (W.C.H. 34082), a 50-year-old Negro, was first admitted to the hospital on September 9, 1945, complaining of intermittent pains in the right lower quadrant and of a lump in the left breast. The abdominal pains, which had occurred at occasional intervals for 5 or 6 years, dating back approximately to the time of the menopause, were described as sharp, intermittent and lasting from 2 to 5 minutes and were unassociated with any genitourinary or gastrointestinal complaints or with any change in position or motion. During the 6 weeks before entry these pains had become more frequent, occurring several times a day, occasionally being associated with slight nausea but never with vomiting. The mass in the left breast had first been noted approximately 2 years before entry. It had grown slowly in size and had produced no symptoms. The patient also complained of occasional low-back aches. She denied any weight loss, anorexia or vaginal discharge.

The family history was extremely interesting in that 5 relatives of her father had died of cancer—1 of carcinoma of the stomach, 2 of carcinoma of the breast and 2 of carcinoma of the rectum.

Physical examination was essentially negative with the exception of the left breast, the abdomen and the pelvis. In the upper and outer quadrant of the left breast there was a palpable, tangerine-sized mass, which was firm, nontender and firmly attached to the adjacent glandular structures and to the overlying skin. There was no bleeding or discharge from the nipple. Palpation of the abdomen revealed a round, firm, nontender grapefruit-sized mass in the left lower quadrant. The right vault was normal, but in the left vault the mass described above could be palpated. On bimanual examination a hard solid mass was palpated in the region of the uterus.

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Laboratory examination was essentially negative except for a red-cell count of 3,700,000 and hemoglobin of 68 per cent.

On September 14 the patient was operated on with a preoperative diagnosis of fibroid uterus, left ovarian cyst and carcinoma of the left breast. Palpation of the abdomen disclosed that the large tumor on the left extending upward to the umbilicus had disappeared. The fibroid uterus, however, as well as the palpable. Through the usual abdominal incision the peritoneum was opened, and a large amount of pus-like material was escaped. The uterus was observed to be adherent to the peritoneum throughout the lower half of the abdomen. The fluid was aspirated; the uterus was elevated and found to contain numerous subserous fibroids varying in size, the largest being at the fundus. This was used as a sentinel, and a large ruptured ovarian cyst was delivered by blunt and sharp dissection from the left broad ligament. The left tube presented a large hydrosalpinx. Both the broad ligament and tube were double clamped distally, and their distal ends were clamped and divided, the mass being removed in toto. A suprapubic hysterectomy was then performed in the usual manner. Following the abdominal opening the tumor of the left breast was removed, together with a large portion of breast tissue. The patient had an uneventful course following this operation.

Some microscopic studies of the breast tumor revealed a primary carcinoma, a left radical mastectomy was performed on the 10th postoperative day. Again the postoperative course was uneventful with the exception of the anemia, which was treated with iron and whole-blood transfusions. The patient was discharged on the 22nd hospital day. After discharge the patient felt well, gradually regained strength and had gained 8 pounds when last seen, 5 months following the first operation.

Gross pathological inspection revealed a funnel-shaped mass measuring 12 by 1.5 by 0.5 cm., with a dull and shaggy surface. The wall was thick and fibrous, at one point measuring 1.5 cm. in thickness. The specimen showed yellow-gray areas resembling caseation. The tumor of the breast measured 12 by 8 by 4 cm., with a deeply pigmented, roughy cut surface, a piece of skin measuring 3 by 2.5 cm. On section the specimen showed a mottled dense yellow-gray surface sharply demarcated from the circumferential tissue. The rest of the breast tissue was abundant, gray and firm.

Microscopic examination of the tube disclosed a soft mass of tumor cells filling the lumen without any attempt at gland formation. Under high-power inspection these cells had an irregular cell membrane. The nuclei were mostly oval and vesicular, with rare nucleoli. Many mitoses and a few stroma cells were seen.

The breast showed strands of tumor cells with little stroma. The cells had poorly staining cytoplasm and dark nuclei. Few mitoses were present. In some areas there were wreaths of consecutive cells.

The diagnosis was primary carcinoma of the fallopian tube and primary medullary carcinoma of the breast.

From a pathological point of view, attention should be drawn to the difficulty in differentiating tuberculosis and carcinoma of the tube. The former pinches off tiny groups of epithelial cells of the mucosa in such a way that they may present a picture that simulates carcinoma. In all cases of tubal carcinoma a search for the giant cells of tuberculosis is therefore essential.

* * *

A few of the more important considerations regarding the incidence, diagnosis and treatment of primary carcinoma of the fallopian tube are discussed.

A report of the first case of this disease diagnosed in this hospital is presented in which the rare primary tubal carcinoma was associated with a primary carcinoma of the breast in a patient whose family history included 5 cases of deaths due to

cancer. Although 30 per cent of cases of primary carcinoma of the fallopian tube are bilateral inasmuch as the diagnosis was made only by routine pathological examination of tissue removed at operation for a fibroid uterus and ovarian cyst, and also because the case was further complicated by a second major operation, a radical mastectomy, it was not deemed advisable to subject the patient to further surgery. X-ray and radium therapy were not given the patient.

REFERENCES

1. Miller, R. M., and Miller, R. W. Primary carcinoma of fallopian tube. *Ann. O. & G.* 50:233-235, 1945.
2. Martin, R. H. Primary cancer of fallopian tube: presentation of a case, diagnosis, clinical, diagnosis, and treatment, with review of cases diagnosed by the operation. *Ann. O. & G.* 40:144-150, 1947.
3. Feltz, J. E. Primary carcinoma of fallopian tube: case report. *St. M. J.* 25:152-153, 1941.
4. Keith, D. J. Primary carcinoma of fallopian tube and ovaries. *Gynecology*, 41:1-2, 1943.

COMPLETE ABSENCE OF LOCHIA FOLLOWING DELIVERY*

REPORT OF A CASE

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THE characteristic bloody discharge that follows childbirth has always been considered such a fundamental phenomenon of parturition that it is designated by the word "lochia," derived from a Greek word meaning "woman in childbirth." Complete absence of lochial discharge following the birth of a viable infant has not, to our knowledge, been reported. In 1922 Kickham¹ reported the case of a patient delivered by cesarean section in which there was no grossly demonstrable cervix or cervical opening, there was no sign of vaginal discharge until fifteen hours post partum, when a thin serous fluid, which gradually became blood stained, appeared and continued to be discharged intermittently until the patient left the hospital twenty-two days later. Sperling² noted that involution occurred more quickly following cesarean section and believed this to be due to a diminished wound surface—in cesarean section only the body of the uterus is wounded whereas in delivery through the pelvis the factors of trauma to the cervix and to the vagina are added. DeLee,³ commenting on Sperling's article, states, "The small amount of lochia after cesarean section is remarkable; indeed one often suspects lochiostasis, and attempts unnecessary drainage." Bardenheuer, who is quoted by Sperling as making the same observation, considered the paucity of lochia to be due

*Presented at a meeting of the Boston Obstetrical Society on January 15, 1946.

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tender. During the following 2 days the splenic tenderness increased, with a concomitant increase in the temperature, which at one time reached 102°F. This splenic tenderness was believed to be caused by a small, traumatic, subcapsular hemorrhage. Within 2 days the perisplenitis decreased slowly until the pain entirely disappeared within a month. The spleen decreased slowly in size but remained palpable at the end of 1 month of treatment. The pigmentation around the eyes was no longer detected at that time. On March 27 examination of the blood revealed a red-cell count of 4,160,000, with a hemoglobin of 80 per cent, and a white-cell count of 9000, the sedimentation rate was 20 mm per hour. The gain in appetite, weight and strength was steady, and the patient was discharged from the hospital on April 13.

A case of visceral leishmaniasis (kala-azar) is reported.

The possibility of visceral leishmaniasis should be considered in patients with fever of undetermined origin, leukopenia and splenomegaly who have resided in an endemic area.

CO-EXISTENT PRIMARY CARCINOMA OF THE FALLOPIAN TUBE AND OF THE BREAST

REPORT OF A CASE

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EDWARD A. KILROY, M.D.†

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THE purpose of this paper is to discuss primary carcinoma of the fallopian tube, and to submit a report of the first case at the Worcester City Hospital of carcinoma of the fallopian tube and carcinoma of the breast in the same patient. As in the vast majority of cases reported in the literature, the diagnosis of tubal carcinoma was not made preoperatively. It was only suspected during the operation for another pelvic disorder and was confirmed by routine pathological study of the tissues removed during the operation.

Since Rokitsansky's original pathological description in 1861 and the first accredited case report presented by Orthmann in 1886, only 449 cases of primary carcinoma of the fallopian tube have been reported in the literature, according to a recent review by Mitchell and Mohler.¹ From figures presented by various clinics these authors estimate that the incidence of the disease among genital-tract tumors is 0.5 per cent, secondary carcinoma of the fallopian tube being about ten times more frequent. The extreme difficulty in diagnosis without pathological studies of the diseased tubes has been discussed by many authors, and it is only with this fact in mind that Martzloff,² allowing for unreported as well as unrecognized cases, estimates the upper limit of incidence of primary tubal cancer to be about 0.5 per cent.

The importance of a serous or serosanguineous discharge from the cervix as a diagnostic aid in this disease has been emphasized by numerous authors.^{3,4} Martzloff² states that if recent gestation and disease of the vagina and uterine cavity — especially incipient ulcerating cancer complicated by cervical stenosis — can be excluded, a copious, serosanguineous uterine discharge becomes suspiciously pathognomonic and can be ascribed to an extrauterine origin, logically tubal, and a malignant complication. The symptom complex of an otherwise unexplained intermittent, cramplike, abdominal discomfort relieved by the passage of a watery discharge from the vagina, especially when blood tinged, has been considered to be of diagnostic value by several authors, including Martzloff² and Mitchell and Mohler.¹ A further adjunct in diagnosis lies in hystero-graphy, whose value and advisability have been debated by different authors.

The treatment of primary tubal carcinoma consists in surgery, with or without postoperative radium or x-ray therapy. Although Martzloff² considered bilateral salpingo-oophorectomy and pan-hysterectomy the operation of choice and believed that there was no evidence that radium and irradiation were of value, other authors have taken exception to his opinions. Keith⁴ proposed the surgical removal of both tubes and ovaries and all pathologic tissue except the uterus, which is left in situ as a receptacle for radium. He believed that good surgery, in addition to the immediate postoperative use of radium implantation and irradiation, would save a larger percentage of patients than either surgery or x-ray therapy alone.

J. H. (WCH 34082), a 50-year-old Negress, was first admitted to the hospital on September 9, 1945, complaining of intermittent pains in the right lower quadrant and of a lump in the left breast. The abdominal pains, which had occurred at occasional intervals for 5 or 6 years, dating back approximately to the time of the menopause, were described as sharp, intermittent and lasting from 2 to 5 minutes and were unassociated with any genitourinary or gastrointestinal complaints or with any change in position or motion. During the 6 weeks before entry these pains had become more frequent, occurring several times a day, occasionally being associated with slight nausea but never with vomiting. The mass in the left breast had first been noted approximately 2 years before entry. It had grown slowly in size and had produced no symptoms. The patient also complained of occasional low-back aches. She denied any weight loss, anorexia or vaginal discharge.

The family history was extremely interesting in that 3 relatives of her father had died of cancer — 1 of carcinoma of the stomach, 2 of carcinoma of the breast and 2 of carcinoma of the rectum.

Physical examination was essentially negative with the exception of the left breast, the abdomen and the pelvis. In the upper and outer quadrant of the left breast there was a palpable, tangerine-sized mass, which was firm, nontender and firmly attached to the adjacent glandular structures and to the overlying skin. There was no bleeding or discharge from the nipple. Palpation of the abdomen revealed a round, firm, nontender grapefruit-sized mass in the left lower quadrant. The right vault was normal, but in the left vault the mass described above could be palpated. On bimanual examination a hard solid mass was palpated in the region of the uterus.

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laboratory examination was essentially negative except a red-cell count of 3,790,000 and hemoglobin of 68 per cent. On September 14 the patient was operated on with a pre-operative diagnosis of fibroid uterus, left ovarian cyst and carcinoma of the left breast. Palpation of the abdomen disclosed that the large tumor on the left extending upward to the umbilicus had disappeared. The fibroid uterus however was still easily palpable. Through the usual subumbilical incision the peritoneum was opened, and a large amount of chocolate-colored fluid escaped. The omentum was observed to be adherent to the peritoneum throughout the lower half of the abdomen. The fluid was syphoned, the uterus was elevated and found to contain numerous subserous fibroids varying in size, the largest being at the fundus. This was used as a nodule and a large ruptured ovarian cyst was delivered blunt and sharp dissection from the left broad ligament. The left tube presented a large hydrophalus. Both the broad ligament and tube were double clamped distally, and their proximal ends were clamped and divided, the mass being removed in toto. A supravaginal hysterectomy was then performed in the usual manner. Following the abdominal operation the tumor of the left breast was removed, together with a large portion of breast tissue. The patient had an uneventful course following this operation.

Since microscopical studies of the breast tumor revealed a primary carcinoma, a left radical mastectomy was performed on the 10th postoperative day. Again, the post-operative course was uneventful with the exception of the anemia, which was treated with iron and whole-blood transfusions. The patient was discharged on the 23rd hospital day. After discharge the patient felt well, gradually regained strength and had gained 8 pounds when last seen, 5 months following the first operation.

Gross pathological inspection revealed a funnel-shaped tube measuring 12 by 2.5 by 0.5 cm., with a dull and shaggy serosa. The wall was thick and fibrous, at one point measuring 1.5 cm. in thickness. The specimen showed yellow-gray necrosis resembling caseation. The tumor of the breast measured 12 by 8 by 4 cm., with a deeply pigmented, roughly elliptical piece of skin measuring 3 by 2.5 cm. On section this specimen showed a mottled, dense, yellow-gray surface sharply demarcated from the circumferential tissue. The rest of the breast tissue was abundant, gray and firm.

Microscopic examination of the tube disclosed a solid mass of tumor cells filling the lumen, without any attempt at gland formation. Under high-power inspection these cells had an indistinct cell membrane. The nuclei were mostly oval and vesicular, with rare nucleoli. Many mitoses and a few stroma cells were seen.

The breast showed strands of tumor cells with little stroma. The cells had poorly staining cytoplasm and dark nuclei. Few mitoses were present. In some areas there were wide bands of connective tissue.

The diagnoses were primary carcinoma of the fallopian tube and primary medullary carcinoma of the breast.

From a pathological point of view, attention should be drawn to the difficulty in differentiating tuberculosis and carcinoma of the tube. The former pinches off tiny groups of epithelial cells of the mucosa in such a way that they may present a picture that simulates carcinoma. In all cases of tubal carcinoma a search for the giant cells of tuberculosis is therefore essential.

* * *

A few of the more important considerations regarding the incidence, diagnosis and treatment of primary carcinoma of the fallopian tube are discussed.

A report of the first case of this disease diagnosed in this hospital is presented in which the rare primary tubal carcinoma was associated with a primary carcinoma of the breast in a patient whose family history included 5 cases of deaths due to

cancer. Although 30 per cent of cases of primary carcinoma of the fallopian tube are bilateral, inasmuch as the diagnosis was made only by routine pathological examination of tissue removed at operation for a fibroid uterus and ovarian cyst, and also because the case was further complicated by a second major operation, a radical mastectomy, it was not deemed advisable to subject the patient to further surgery. X-ray and radium therapy were not given the patient.

REFERENCES

- 1 Mitchell R M and Mohler R W. Primary carcinoma of fallopian tube. *Am J Obst & Gynec* 50:28-292 1945
- 2 Martzloff K H. Primary cancer of fallopian tube: consideration of its incidence, clinical diagnosis and treatment with report of case diagnosed before operation. *Am J Obst & Gynec* 40:804-821 1940
- 3 Hobbs J E. Primary carcinoma of fallopian tube: case report. *South M J* 35:753-757 1942
- 4 Keith D Y. Primary carcinoma of fallopian tubes and ovaries. *Kentucky M J* 41:74-79 1945

COMPLETE ABSENCE OF LOCHIA FOLLOWING DELIVERY*

REPORT OF A CASE

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THE characteristic bloody discharge that follows childbirth has always been considered such a fundamental phenomenon of parturition that it is designated by the word "lochia," derived from a Greek word meaning "woman in childbed." Complete absence of lochial discharge following the birth of a viable infant has not, to our knowledge, been reported. In 1922 Kichham¹ reported the case of a patient delivered by cesarean section in which there was no grossly demonstrable cervix or cervical opening, there was no sign of vaginal discharge until fifteen hours post partum, when a thin serous fluid, which gradually became blood stained, appeared and continued to be discharged intermittently until the patient left the hospital twenty-two days later. Sperling² noted that involution occurred more quickly following cesarean section, and believed this to be due to a diminished wound surface—in cesarean section only the body of the uterus is wounded, whereas in delivery through the pelvis the factors of trauma to the cervix and to the vagina are added. DeLee,³ commenting on Sperling's article, states, "The small amount of lochia after cesarean section is remarkable, indeed, one often suspects lochiostasis, and attempts unnecessary drainage." Bardenhauer, who is quoted by Sperling as making the same observation, considered the paucity of lochia to be due

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to acidosis and mentioned an attempt to control the amount of lochia by diet

In the following case, in which the patient was delivered by cesarean section at thirty-six weeks because of toxemia, a contracted pelvis, elderly primiparity and a breech presentation, there was no vaginal discharge during the twenty-one days of an otherwise normal postoperative and puerperal course. During that time the temperature rose above normal on three scattered occasions, but never above 99.4°F

Mrs. C, a 40-year-old primigravida, was first seen during the 12th week of pregnancy. There had been no serious illnesses and no operations. The periods, which had begun at the age of 12 years, occurred regularly every 28 days, but the flow for the preceding 10 years had been scanty and of only 2 days' duration. The last regular period had begun on July 24, 1944. Physical examination revealed no abnormalities. The blood pressure was 138/86, and urinalysis was negative.

The pregnancy continued uneventfully until the 34th week of gestation, when there was an elevation of blood pressure to 142/110, urinalysis revealed the smallest possible trace of albumin, and there was slight edema of the hands and ankles. The patient was treated at home for a week with bed rest, mild sedation, a salt-free diet and saline catharsis. This treatment brought no improvement, and the patient was admitted to the Cardinal O'Connell House, St. Elizabeth's Hospital. The blood pressure was then 150/114. The urine showed a trace of albumin, and the edema had increased. After a week of complete bed rest, sedation, saline purgation and intravenous hypertonic dehydration, the blood pressure had risen to 178/114. The patient became irritable and apprehensive, and there was upper abdominal distress and headache. She was then 36 weeks pregnant. The fundus was palpated 3 fingerbreadths below the ensiform. The fetus was in the left sacroanterior position, with the breech in the false pelvis. The pelvic outlet was narrow, and the cervix long and firm.

On March 31, 1945, after a transverse cervical cesarean section under spinal anesthesia, a female infant weighing 4 pounds, 14 ounces was delivered. The infant was otherwise normal in all respects and was discharged from the hospital in 35 days, weighing 5 pounds, 9 ounces. The infant was not breast fed. One ampule of ergot was administered intramuscularly following delivery. The intravenous route was not used because of the mother's hypertension. The placenta and membranes were expressed intact after they had begun to separate.

On the following day the blood pressure had dropped to 114/96. The temperature was 99.4°F, the pulse 84, and the respirations 20. There was no nausea or vomiting. The edema had disappeared, the patient felt well and was excreting a normal amount of urine. Since returning from the operating room there had been absolutely no lochial discharge. The fundus was nontender and firm, and could be felt 1 fingerbreadth below the umbilicus. The temperature on the 1st, 4th and 10th post-partum days was slightly elevated, the highest reading was 99.4°F. The postoperative course was otherwise entirely uneventful. The patient was allowed out of bed on the 7th postoperative day.

There was no distention and no elevation of pulse or respirations. The vulval pads were carefully inspected and remained perfectly dry until discharge from the hospital. The fundus, which was felt each day, continued to be nontender, and involution progressed normally, so that the fundus was felt 3 fingerbreadths above the symphysis on the 12th post-partum day. The patient was discharged on the following day, when the blood pressure was 120/90 diastolic.

On the 21st day following delivery, menstrual flow began. The amount of flow was slightly more profuse and lasted 1 day longer than the usual period. The flowing was painless, and there were no clots. On examination, 4 weeks after delivery, the fundus was in anterior position, and was $\frac{1}{2}$ larger than normal. There was no vaginal discharge, and the general condition was excellent. Two weeks later the uterus was normal in size and position. There was no discharge, and the urine was normal. The blood pressure was 124/84.

Fifteen weeks after delivery, the blood pressure was 128/78, urinalysis was negative, the fundus was normal in size and position, and the patient felt well. The periods, which were scanty and of 2 days' duration, had occurred regularly at 28-day intervals.

Involution, the change in the size of the uterus following delivery, is one of the most striking examples of atrophy known. The average post-partum uterus is said to weigh in the vicinity of $2\frac{1}{2}$ pounds, or 1000 gm,⁴ half as much a week later, from 350 to 375 gm at two weeks and 50 gm when normally involuted at six or seven weeks. The structures involved in this process are the muscle fibers, the blood vessels and the decidua, especially at the placental site. The amount of lochia has been variously estimated as between 500 and 1000 cc,⁵ although we have found no record of accurate measurement, during the first three days it is said to be profuse enough to soak a perineal pad in six to eight hours.⁶ The bloody discharge is generally believed to last from ten days to two weeks.

Knowledge concerning the processes of regeneration of the uterine mucosa following labor may be said to have begun with the monograph of Friedlander,⁷ written in 1870, although William Hunter,⁸ a century earlier, had stated that "the decidua is an efflorescence of the inner coat of the uterus, and is therefore shed as often as the woman bears a child or suffers a miscarriage." In 1931 Williams⁹ described in detail the regeneration of the uterine mucosa following delivery, he stated that the cervical mucosa is not cast off and is completely restored by the end of the first week post partum, although the tissue beneath it may long remain infiltrated with blood, he also observed that, at the end of fourteen days, the uterine cavity is completely covered by endometrium and that by the third week the uterine mucosa is entirely restored, with the exception of the placental site, which disappears in about seven weeks. These changes are brought about by encapsulation, by orderly invasion and, finally, by exfoliation by sensible and insensible lochial discharge and fibrolysis. Since the noticeable lochial discharge continues for about two weeks and the regeneration of the placental site is not complete for seven weeks (and only then by a process of exfoliation), it is evident that this material must disappear by some lytic action that causes either its absorption or its insensible discharge. To explain this part of the regeneration Jochman¹⁰ postulated the presence of a proteolytic enzyme in the lochia, and both Irving¹¹ and Beck¹² mentioned a breakdown of protoplasm during the puerperium into simpler substances that are eventually excreted by the kidneys, as evidenced by the fact that nitrogen elimination is doubled during that time.

A possible explanation of the case reported above is that the patient was an elderly primigravida whose past history of short, scanty periods indicated a thin endometrium. It has been shown by Rock¹³ that in

these cases the predecidua — and, it is assumed in pregnancy the decidua as well — is less thick than that usually found, although the cytology denotes the estrogen-progesterone relations to be normal. In other words, there is simply a paucity of normal tissue and no interference with fertility. It is possible that the predecidua and decidua in the case presented were of this type. The amazing rapidity with which the endometrial epithelium covers the denuded menstrual surface of the uterus is known, and the process is believed to start before the patient has stopped flowing. In 1901 Krönig¹⁴ pointed out that, although separation of the placenta and membranes usually occurs in the spongy layer of the decidua, it does not occur as schematically as described in the literature, and he showed that the amount of tissue retained varies greatly, consisting in some places of only a few layers of cells and in others of portions of spongy layer measuring several millimeters in thickness. In 1917, after studying 50 cases in which the uterus had been removed at cesarean section, Williams⁹ concluded that whereas separation generally occurs in the spongy layer, the line of cleavage is extremely irregular, so that in some places a thick layer of decidua and in others only a few layers of cells remain and that in still others the muscularis is practically bare.

In the case presented above it is possible that, at the time the placenta and membranes were expressed after they had begun to separate, there was little decidua left and that what remained was disposed of by rapid autolysis accompanied by a speedy regeneration of the mucosa. After twenty-one days there was probably some bleeding from the placental site in the process of exfoliation, as noted in 60 per

cent of cases by DeLee,¹⁵ with a subsequent resumption of normal menstrual cycles.

* * *

The case of a forty-year-old primigravida delivered by cesarean section four weeks before term is presented. There was complete absence of lochia throughout the puerperium. In other respects, the post-partum course was quite uneventful, and the uterus involuted normally.

A possible explanation for the absence of the lochial discharge is discussed.

The data presented indicate that complete absence of the lochia is compatible with a normal puerperium. Dilatation of the cervix or other operative intervention is contraindicated unless symptoms clearly indicate their necessity.

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REFERENCES

1. Kichham C J. Pregnancy without demonstrable cervix or cervical canal with report of case. *Boston M & S J* 187:732 1922.
2. Sperling W. Über Uterusinvolution und Wochenfluss nach Kaiserschnittoperationen sowie bei Wochenrinnen mit saurer und mit gemischter Kost. *Zentralbl f Gynäk* 58:2015-2015 1934.
3. *Year Book of Obstetrics and Gynecology*. Edited by J B DeLee and J P Greenhill. 6 vol. Chicago: Year Book Publishers Incorporated 1934. P 261.
4. Lutzenberg J C. *Synopsis of Obstetrics*. 794 pp. St. Louis: C V Mosby Company 1940. P 149.
5. Bourne A W. *Synopsis of Obstetrics and Gynecology*. 452 pp. Baltimore: William Wood & Company 1927. P 186.
6. Reynolds E. *Practical Midwifery*. 405 pp. New York: William Wood & Company, 1897. P 359.
7. Friedlander. Cited by Williams. P 664.
8. Hunter. Cited by Williams. P 664.
9. Williams J W. Regeneration of uterine mucosa after delivery with especial reference to placental site. *Am J Obs. & Gynec* 22:664-696 1931.
10. Jochman G. Über die Bedeutung des proteolytischen Leukocytenfermentes in Lochialsecret und im Colostrum sowie über den Antirypsingehalt im Serum der Wochenrinnen. *Arch. f Gynäk* 89:508-516 1909.
11. Irving F C. *A Textbook of Obstetrics for Students and Practitioners*. 558 pp. New York: The Macmillan Company 1936. P 173.
12. Beck A C. *Obstetrical Practice*. Second edition. 858 pp. Baltimore: Williams & Wilkins Company 1939. P 328.
13. Rock J. Menstruation its disorders and their treatment. *New Eng J Med* 233:817-824 1945.
14. Krönig. Cited by Williams. P 668.
15. DeLee J B. *The Principles and Practice of Obstetrics*. Seventh edition. 1211 pp. Philadelphia: W B Saunders Company 1938. P 244.

MEDICAL PROGRESS

THE PHYSIOLOGIC AND CLINICAL SIGNIFICANCE OF PLASMA PROTEINS AND PROTEIN METABOLITES (Concluded)*

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CIRCULATING PROTEIN METABOLITES

The circulating plasma proteins represent one phase in the dynamic equilibrium existing between plasma and tissue proteins. Another clinically important phase of protein metabolism in health and disease is associated with the circulating protein catabolites. These nonprotein nitrogenous substances are the resultants of intermediary metabolism of ingested and tissue proteins. The nonprotein nitrogen of the blood—that portion not precipitated by the usual protein precipitants—is a heterogeneous mixture of urea, uric acid, amino acids, creatine, creatinine and a fraction designated as “undetermined nitrogen” that appears to contain polypeptides, various amino acids, adenylic-nucleotide and other components.¹⁰³ The relative concentration ranges of these substances are indicated in Table 7.

Most of the end products of nitrogen metabolism are removed in the urine. An inadequate rate of excretion, whether the result of decreased blood

Changes in blood nonprotein nitrogen may reflect altered concentration of any of its constituents. Most frequently, marked changes are the result of alterations in urea or undetermined nitrogen, or both. Creatine, creatinine, uric acid and amino acid nitrogen concentrations in the blood are relatively small. Fluctuations are usually not attended by marked changes in the nonprotein nitrogen. Increased nitrogen retention, or azotemia, is the resultant of the rate of nitrogen catabolism, hydration, urine volume, nitrogen excretion and mineral metabolism. Azotemia, therefore, is not in itself necessarily indicative of renal damage or permanently impaired renal function. Several conditions that may be associated with altered concentrations of blood nonprotein nitrogenous constituents are listed in Table 8, and detailed discussions of this subject are available in several texts.^{20, 103}

Urea is the chief nitrogenous end product of protein metabolism in mammals. Urea so formed does not enter into further metabolic reactions. The experiments of Bollman, Mann and Magath¹⁰⁴ with hepatectomized dogs demonstrated that the liver was the principal site of urea formation. The bulk of the nitrogen for urea synthesis is derived from the amino nitrogen of the amino acids. Nitrogen from other sources—such as ammonia, absorbed deamination products, amide and other groupings—may be converted into urea. Urea synthesis involves the cyclical participation of several amino acids (arginine, citrulline, ornithine and glutamine), enzymes (arginase), ammonia, carbon dioxide and bicarbonate.¹²⁶⁻¹²⁸ Interrelations between arginine and ornithine in the process of urea formation have been confirmed by isotopic analysis,⁵ but do not completely explain the process of urea formation.¹²⁹ Complete details concerning this fundamental process are as yet unknown.

Urea nitrogen comprises approximately 80 per cent of excreted urinary nitrogen. Urea is a readily diffusible nonelectrolyte and appears in relatively equal proportions throughout the body fluids and tissues.¹⁰³ Clearance of urea from the blood more accurately depicts renal function than blood urea nitrogen concentration. An increase in the urea nitrogen-nonprotein nitrogen ratio may provide a fair indication of decreased urea clearance.¹³⁰ Increased blood urea nitrogen may be the primary result of altered renal structure and function—as

TABLE 7 Relative Concentration Ranges of Blood Nonprotein Nitrogenous Constituents*

CONSTITUENT	PLASMA	BLOOD CORPUSCLES	WHOLE BLOOD
	mg/100 cc	mg/100 cc	mg/100 cc
Urea nitrogen	13-23 ¹¹⁶	12-22 ¹¹⁶	5-23 ¹¹⁷
Amino acid nitrogen	3-5-6 ¹¹⁶ 110	8-9-13 ¹²¹	5-8 ¹⁰³
Creatine	0-1-0 5122 123	4-8 ¹¹⁶	4-9
Creatinine	1-1 7122 123	1-3 ¹¹⁶	1-2 ¹⁰³
Uric acid nitrogen	2-6 ¹²⁴	1-4 ¹¹⁶	2-4 ²⁰
Ammonia nitrogen	—	—	0-1-0 3103
Undetermined nitrogen	21 ¹⁸	19 ¹¹⁶	5-19 ¹⁰³
Total nonprotein nitrogen	20-36 ¹¹⁶	39-61 ¹¹⁶	25-40 ¹⁰³

*Relative ranges are somewhat modified by the method of chemical analysis, metabolic state and preceding dietary pattern of the subject. In some cases the age, sex and physiologic state influence the normal ranges (amino acid nitrogen, creatine, creatinine and uric acid nitrogen).

flow or of reduction in the proportion of protein metabolites removed, is manifested as reduced clearance of these substances from the blood. The ultimate clinical equivalent is retention of nonprotein nitrogen constituents. The significance of these substances in blood rather than in urine is briefly discussed below.

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TABLE 8 Conditions* Associated with Altered Concentrations of Blood Nonprotein Nitrogenous Constituents †

BLOOD UREA NITROGEN INCREASED CONCENTRATION	AMINO ACID NITROGEN INCREASED CONCENTRATION	URIC ACID NITROGEN INCREASED CONCENTRATION	CREATINE INCREASED CONCENTRATION	CREATININE INCREASED CONCENTRATION
Decreased renal urea excretion Glomerulonephritis Congenital renal abnormalities Hypogenesis Hypoplasia Polycystic disease Local destruction or inflammation Pyelonephritis Pyonephrosis Nephrosclerosis Cancer Tuberculosis Urinary obstruction Tubule edema Serum disease Mercury poisoning Tubule obstruction Sulfonamide crystals Urares Hemoglobin Bence-Jones protein Amyloid deposits Cylindruria Ureteral or urethral lithiasis Prostatic hypertrophy Carcinoma	Decreased deamination Acute hepatic insufficiency Acute yellow atrophy Toxic necrosis Hepatic carcinoma Thermal burns Increased availability or catabolism Intravenous amino acid infusion (transient) Hormone administration (variable) Anterior pituitary Thyroxine Adrenocortico-sterone Testosterone Leukemia Polycythemia vera Decreased renal function Hepatorenal syndrome Eclampsia Hemorrhagic shock (†) Ablation of renal function	Abnormal purine metabolism Gout Increased nucleoprotein metabolism Leukemia Multiple myeloma Polycythemia vera Pernicious anemia (in remission) Renal abnormalities Nephritis Nephrosclerosis Essential hypertension Lead poisoning Eclampsia Miscellaneous Cardiac decompensation Pneumonia Acute hepatic necrosis Osteoarthritis	Increased catabolism Hyperthyroidism Progressive muscular atrophy Muscular atrophy Hormone administration (methyl testosterone) Starvation Increased synthesis High protein diet Miscellaneous Intravenous amino acid infusion (if serum creatine previously elevated)	Renal insufficiency Nephritis Urologic obstruction (rare)
Decreased urine volume (prerenal deviation of water) Shock and hemoconcentration Burns Upper gastrointestinal obstruction Pancreatic fistula Peritonitis Constrictive pericarditis Congestive failure with decreased renal blood flow Addison's disease Prolonged vomiting Prolonged diarrhea Dehydration Acidosis				
Excessive protein catabolism Severe toxic and febrile diseases (infections) Severe thyrotoxicosis Starvation Marked protein deficiency				
Miscellaneous factors Hepatorenal syndrome Diabetic acidosis Gout Severe hyperparathyroidism Upper gastrointestinal hemorrhage Ulcer Vancer Cancer Infectious diseases, typhus pneumonia and so forth Eclampsia				
DECREASED CONCENTRATION	DECREASED CONCENTRATION	DECREASED CONCENTRATION	DECREASED CONCENTRATION	DECREASED CONCENTRATION
Decreased urea synthesis Acute hepatic insufficiency Acute yellow atrophy Toxic necrosis Phosphorus carbon tetrachloride arsenamine and cinchophen poisoning Extensive hepatic degeneration Cirrhosis Cancer Normal pregnancy	Increased demand Pneumococcal pneumonia Nephrosis (in children) Hormone administration Insulin Adrenalin	Decreased concentrations not clinically significant	Decreased concentrations not clinically significant	Decreased concentration not clinically significant

*Tabulated by supplementation of original compilation of Peters and Van Slyke¹⁰² Physiologic variations not tabulated
†Variations in total nonprotein nitrogen of blood not tabulated. Such variation is the summation of contributing variables. Most frequently increased nonprotein nitrogen reflects increased blood urea nitrogen and undetermined nitrogen. It is apparent that in some cases other constituents may be involved. Variations of undetermined nitrogen are not tabulated.

in the nephritides — or may occur in the presence of essentially normal renal structure with either normal or temporarily abnormal function ("prerenal azotemia") — as in gastrointestinal hemorrhage or typhus fever. Pathologic variations occurring in several diseases are indicated in Table 8.

Protein metabolism is essentially the metabolism of the amino acids.¹⁰³ Amino acids absorbed from the intestine — neither deaminated nor synthesized into protein by the liver and supplemented by similar fractions derived from the constant interchange of dietary and tissue protein — constitute the circulating amino acid nitrogen of blood. The amino acid nitrogen concentration of plasma remains quite constant at a level approximating 3 to 6 mg per 100 cc.¹¹⁹ Transient physiologic increases occur following ingestion of a protein meal or parenteral amino acid administration. The liver is the primary site of the deamination of amino acids, and approximately 90 per cent of its functional capacity must be interfered with before deamination is impeded. When urea forming or deaminizing functions of the liver are impaired, the blood amino acid nitrogen increases and the blood urea nitrogen decreases. Urinary amino acid excretion correspondingly increases. With extensive hepatic damage, leucine and tyrosine crystals may be identified in the urine.^{103, 131} Specific amino acid excretion in the urine may occur with rare congenital defects in amino acid metabolism. A partial list of diseases associated with pathologic alterations in amino acid nitrogen is indicated in Table 8. Parenteral administration of amino acid hydrolysates induces a moderate transient increase in blood amino acid and urea nitrogen. Patients with previously elevated serum creatines and associated alterations in utilization or disposal of creatine may evidence a further increase in serum creatine following amino acid administration. The increased creatine is probably derived from the methionine and arginine of the hydrolysate.¹³² Decreases in serum inorganic phosphate attendant to parenteral amino acid administration have been observed.¹³³ A rapid increase of amino acid nitrogen to levels greater than 10 mg per 100 cc on infusion of an amino acid digest may be associated with nausea and vomiting. Glutamic or aspartic acids may be responsible for this phenomenon.¹³³ An increase in plasma amino acid nitrogen (in rats) associated with peripheral circulatory failure and hemorrhagic shock presumably affords an unfavorable prognostic sign.¹³⁴ Elevation of the plasma alpha amino nitrogen levels has been observed in thermal burns.¹³⁵

Creatinine, another component of the nonprotein nitrogen of the blood, is the anhydride of creatine. The formation of creatinine from creatine may proceed without intermediate steps¹³⁶ or may be related to phosphocreatine.¹³⁷ Isotopic technics have indicated that creatine formation is dependent on the formation and methylation of glycocyamine. Choline

or methionine constitutes the principal source of methyl groups.¹³⁸ The nitrogenous constituents of creatine appear to be derived from glycine and arginine.⁵ It is thus apparent that the metabolism of creatine is closely related to choline and at least two amino acids — methionine and arginine. Blood creatine concentration in health is usually constant and clinically insignificant. It may be increased in hyperthyroidism,¹²³ various severe or terminal illnesses and, if initially elevated, following infusion of an enzymatic hydrolysate of casein.¹³² Blood creatinine concentration may vary considerably in disease. Increased concentration may occur in any disease in which marked nonprotein nitrogen retention occurs. Markedly increased blood creatine and creatinine are probably the result of increased endogenous protein catabolism in addition to some degree of impaired excretion. Variation in the rate of excretion of creatine or of creatinine may result from changes in the rate of synthesis of creatine from its precursors, in the ability of tissues to store or to liberate creatine or in the rate or direction of creatine-phosphocreatine reactions.¹³⁹

Uric acid, in man, is the chief end product of exogenous and endogenous nucleoprotein metabolism. In both its synthesis and its excretion, uric acid is closely associated with the amino acids. Glycine, alanine, aspartic, glutamic and pyruvic acids increase uric acid excretion, benzoic and phenylacetic acids depress its excretion. Details of uric acid metabolism remain obscure.¹⁴⁰ The normal concentration of blood uric acid (2 to 6 mg per 100 cc) is little affected by purine-rich foods and is not directly related to the level of nonprotein nitrogen or urea. Abnormal increases of blood uric acid may occur in association with decreased urate elimination by the kidney, primary alterations in nucleoprotein metabolism such as gout, increased endogenous nucleoprotein catabolism as in leukemia or pernicious anemia or excessive nucleoprotein or purine supply associated with these metabolic defects. Destruction of uric acid does not appear to take place in human beings. Like other nonprotein nitrogen catabolites, uric acid is excreted preponderantly in the urine. Urates are freely diffusible, are equally distributed in plasma and glomerular urine and are limitedly concentrated by the tubules. The low tubular concentrating power accounts for the relatively high blood uric acid concentration.¹⁴¹ Uric acid excretion is related to urinary volume and may be increased by the diuresis attendant to continuous infusion of glucose with maintained hyperglycemia.¹⁴² Functional inhibition of urate excretion may explain hyperuricemia. The etiology of tissue urate deposits remains unknown. Hyperuricemia, local trauma, infectious agents, circulatory impairment and primary local tissue changes favor urate precipitation.¹⁴¹ Uricemia associated with several pathologic states is indicated in Table 8.

Ammonia, another of the nitrogenous end products of protein metabolism, results from kidney deamination of alpha-amino groups of amino acids. Dietary ammonia derived from protein digestion products is not a source, and urea is not an intermediate in ammonia formation.⁵ Since the ammonia nitrogen concentration of blood is quite small (less than 0.3 mg per 100 cc) and since conditions that produce a marked increase in urinary ammonia excretion do not appreciably alter blood concentrations,¹⁰³ blood or plasma ammonia nitrogen appears to be of little clinical importance. Urinary ammonia excretion, on the other hand, is of considerable clinical significance, since it represents an attempt to conserve body base.¹⁴³

Undetermined, or residual, nitrogen comprises the final group of nonprotein nitrogenous substances resulting from protein metabolism. Undetermined nitrogen, apparently a cellular component, is said to be composed of hippuric acid, nucleotides and histones.²⁰ Its clinical and metabolic significance is not clear, although a rather large European literature has accumulated. Undetermined nitrogen is usually elevated in disturbances that cause nitrogen retention. In some cases undetermined nitrogen — for practical purposes the difference between urea nitrogen, creatinine nitrogen and the total nonprotein nitrogen — may be of clinical significance. For example, hemorrhage into the gastrointestinal tract is associated with azotemia, which appears to be largely the result of absorption of nitrogenous components from the enteral blood.^{144, 145} Impaired renal function may also be a factor.¹⁴⁶ Continued elevation of the blood urea nitrogen may have prognostic significance.¹⁴⁵ Proportional increases in the undetermined nitrogen fraction may be as great as or greater than increases in urea nitrogen per se and may afford a means of detecting continued gastrointestinal hemorrhage. The azotemia of intestinal obstruction is said to be more closely related to undetermined nitrogen than to urea.¹⁴⁷ In some cases of eclampsia or chronic nephritis with nitrogen retention, undetermined nitrogen may represent the greatest proportional increase in nonprotein nitrogenous substances.²⁰

AMINO ACID AND NITROGEN METABOLISM

The anabolic phase of protein metabolism, that of protein synthesis, was long considered a relatively static process largely restricted in the adult to replacement of the endogenous protein loss of "wear and tear." It was believed by some that body protein was composed of two distinct categories: fundamental structural tissue protein and the more readily utilizable deposit protein of cells and extracellular fluid. It was thought that tissue protein, once formed, remained relatively unchanged until destroyed by metabolic wear and tear. Acute negative nitrogen balance and hypoproteinemia were considered manifestations of deposit protein with-

drawal. The current concept of protein metabolism was evolved from two sources: the suggestion that intracellular protein undergoes continuous change during nitrogen equilibrium at a rate commensurate with nitrogen intake and utilization¹⁴⁸; and observations on plasma protein regeneration and nitrogen balance in the bled, protein-depleted dog subsequent to protein feeding.¹ This theory postulates a continuous dynamic exchange of tissue and plasma proteins.^{1, 2} Direct verification and extension of this concept at the fundamental level of molecular regeneration, involving the constant transfer of specific chemical groups, was obtained by using specific amino acids labeled with isotopes.⁵ Nitrogen in several amino acids was replaced by a heavy atomic analog or isotope, and in some cases, hydrogen of the amino acid carbon chain was also replaced by its heavy isotope, deuterium. By tracing the course of these tagged groups throughout the body, it became evident that both amino nitrogen and the remainder of the amino acid were incorporated in many tissue proteins of the body, including those of the plasma and erythrocyte. It was demonstrated that transfer of entire chemical groups between the various fed and in situ tissue amino acids, as well as their metabolites, constantly occurred. It was inferred that the peptide bonds, which are the chief links binding amino acids into protein structures, are not fixed but rather are rapidly exchanging one constituent group for another. These demonstrated metabolic exchanges, involving both degradation and synthesis, imply enzymatic reactions. Such reactions are not isolated events. Each requires the simultaneous occurrence of others — for example, creatine formation involves groups derived from at least three different amino acids. Two of these amino acids promptly replace their lost fragments from others; other reactions involve cycles, such as urea formation. These metabolic exchanges constitute a fundamental part of the biologic process.⁵

Development of the concept of dynamic equilibrium between tissue and plasma proteins has been attended by observations pertaining to other fundamental roles of certain amino acids in metabolism. The early experimental observations of Osborne and Mendel⁴⁹ provided evidence that two amino acids (lysine and tryptophane) were essential for growth of the rat. This work was extended by the use of diets containing some twenty purified amino acids. When appropriate mixtures were fed to young rats, growth was maintained; in older rats, weight and health were maintained. Omission of individual amino acids indicated that some were indispensable for growth and maintenance and that others were not. By these criteria, a group of ten amino acids were found to be essential for growth of the rat.³ Nitrogen balance studies, utilizing synthetic diets, were extended to adult man and culminated in the observations that only eight amino acids were essential for maintenance of nitrogen

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The continuous formation of plasma proteins is dependent on the supply and adequacy of amino acids and the integrity of their synthesis. Information pertaining to the amino acid composition of

and that associated with antibody formation and immune response may involve different amino acids in varying degrees. On the other hand, amino acid contributions derived from injection of whole blood,

TABLE 10 *Metabolic Implications of the Essential Amino Acids*

AMINO ACID	GENERAL CLASSIFICATION	HUMAN PLASMA COMPOSITION*		KNOWN METABOLIC FUNCTIONS†	CLINICAL SIGNIFICANCE‡
		ALBUMIN %	GLOBULIN %		
Leucine	Mono-amino	11.9	8.9-9.3	May contribute to acetone-body formation in rat ¹⁶⁵ by conversion to trihydroxybutyric acid; carbon chain indispensable	Presumably ketogenic
Isoleucine	-	2.0 ¹⁶⁵	?	May contribute to either acetone-body formation or glycogen deposition under appropriate conditions ¹⁶⁶	Possible limiting factor in human albumin ¹⁶⁷ and plasma therapy
Valine	-	4.1 ¹⁶⁵	?	Glycogenic; decreases experimental ketosis in rats	Deprivation in rats leads to hyperesthesia and severe unco-ordination ¹⁶⁸
Lysine	Di-basic	5.8	6.7	Unlike other amino acids does not readily undergo reamination; therefore presumably represents isolated example of amino acid not reversibly involved in the nitrogen shift; unlike other essential amino acids cannot be replaced by any of its deamination products in metabolism ⁵	Forms cadaverine; a ptomaine on decarboxylation; this is probably of little clinical significance ¹⁷⁰
Arginine	-	6.15	4.8-5.6	Forms ornithine and urea — both concerned in mechanism of urea formation ¹⁷² ; one of precursors of creatine ¹⁷⁶ and probably glutamic acid	Deficiency may impede spermatogenesis ¹⁷¹
Histidine	-	3.5	2.5	Splitting of carbon chain catalyzed by enzymes may yield glutamic acid or histamine or both	Constituent of normal pregnancy urine but not pathognomonic of pregnancy; its elaboration not essential for maintenance of positive nitrogen balance in man (hence dispensable)
Threonine	Hydroxy	5.03	7.3-8.3	May be glycogenic; appears to decrease experimental ketonuria in rat.	
Tryptophane	Aromatic heterocyclic	0.19	2.1-2.9	Metabolic precursor of kynurenic acid and indican which may be normal urinary constituents; and possibly one of precursors of urinary pigment urochrome; intestinal bacterial flora produce indole and skatole from this amino acid	Odor of feces; deficiency leads to cataract formation in the rat ¹⁷² ; human albumin deficient in tryptophane ¹⁷³
Phenylalanine	Aromatic	7.5 ¹⁶⁵	5.9 ¹⁶⁵	May be converted to tyrosine or pursue another metabolic path to phenylpyruvic acid; when converted to tyrosine becomes implicated in synthesis of melanin (skin pigment); tyrosine (diiodotyrosine) and adrenaline; defect in conversion of phenylalanine to tyrosine may be associated with ascorbic acid metabolism (vitamin C) ¹⁷⁴ particularly in premature infants	Albinism may result from enzymic failure of melanin production; alcaptonuria results from incomplete metabolism of phenylalanine and tyrosine and is result of homogentisic acid excretion in urine; oligophrenic phenylpyruvica probably represents failure of conversion of phenylalanine to tyrosine ¹⁷⁴ and is associated with mental deficiency and neurologic stigmas
Methionine	Sulfur-containing	1.28	1.1-1.5	Methionine sulfur may be converted to cystine sulfur ⁵ by relation to cystine; may be implicated in glutathione formation which is important respiratory enzyme; may be precursor of taurocholic bile component by contributing methyl groups; is associated with <i>in vivo</i> synthesis of choline and creatine ⁵ ; if converted to cystine or by contributing methyl groups may be involved in certain detoxication phenomena	Insulin contains cystine; methyl group deficiency may result in fatty livers and abnormal creatine metabolism; deficiency is associated with susceptibility of rat to virus of infectious hepatitis ¹⁷⁵ ; bromobenzene detoxication; cystinuria is congenital defect of cystine metabolism; is involved in conjugation of benzoic to hippuric acid.

*Data pertaining to the amino acid composition of protein is limited by the inadequacy of present analytic methods. The major part of the plasma protein composition data is derived from Brand, Kassel, and Saidel.⁸² The figures for globulin represent values determined for purified gamma globulin and fraction III-2 (beta) globulin.

†All amino acids undergo deamination yielding amino and other groups to the body metabolic pool.

‡Specific clinical significance except that pertaining to maintenance of nitrogen balance and certain congenital defects is not well known at present.

plasma protein, therefore, has clinical importance. The protein depletion and requirement attendant to burns, that occurring in response to various diseases, such as malnutrition, nephrosis or hepatitis,

plasma or plasma fractions may vary. The partial amino acid composition of the major plasma protein components has been tentatively stated.⁸² Albumin contains at least five and probably six essential

equilibrium during the periods of observation^{3, 4} (Table 9)

Nitrogen balance describes the relation between nitrogen intake and output. Positive balance means that less nitrogen is lost from the body than is taken in — nitrogen is being stored. Negative nitrogen balance is exactly the opposite. A positive nitrogen balance represents a desirable state of retention and utilization of protein. The metabolism of amino

TABLE 9 *Indispensable or Essential Amino Acids **

IN RATS	IN MAN
Leucine	Leucine
Isoleucine	Isoleucine
Valine	Valine
Lysine	Lysine
Arginine†	—
Histidine	—
Threonine	Threonine
Tryptophane	Tryptophane
Phenylalanine	Phenylalanine
Methionine	Methionine

*Classification of the usual 22 amino acids as essential or nonessential has resulted largely from the work of Rose³ and his colleagues. In rats an essential amino acid is defined as "one which cannot be synthesized by the animal organism out of the materials ordinarily available, at a speed commensurate with the demands for normal growth."

In man nitrogen balance studies in young adults have been the principal technique used to examine the essentiality of amino acids.⁴

†Arginine can be slowly synthesized by the rat, but not at a sufficiently rapid rate to maintain reasonably good growth.

acids and proteins is partially reflected in the nitrogen balance of the individual. Normal growth¹⁵⁰ and maintenance¹⁵¹ are associated with positive nitrogen balances. Various pathologic states are associated with a loss of nitrogen in their acute or chronic phases, or both.^{152, 153} The negative nitrogen balances observed in these conditions are rather difficult to explain. Apparently, negative balance is not the direct result of diminished protein absorption, disuse atrophy, local toxic tissue destruction, accelerated energy expenditure or heat production or the degree of febrile reaction. Protein metabolic pathways may be distorted, and protein synthesis diminished. The duration and degree of retarded protein synthesis presumably varies inversely with the previous nutritional state and directly with the severity of the disease or injury. It may represent a reparative rather than a primarily destructive process.¹⁵³ Nitrogen lost in such conditions is thought to be derived primarily from tissue protein. This nitrogen loss may be influenced by endocrinologic interrelations. The effect of anterior pituitary growth hormone on nitrogen metabolism in the growing child is well known. Androgens, such as testosterone propionate, initiate nitrogen retention in normal men and women,¹⁵⁴ as well as in eunuchoidal males,¹⁵⁵ and have been observed to induce nitrogen retention in a female patient with Cushing's syndrome.¹⁵⁶ Such hormone administration appears to exert a somatotrophic effect on protein deposition, being associated with decreased urinary excretion of phosphorus, potassium and creatine. Despite quantitative nitrogen retention associated with the

administration of chorionic gonadotropin, testosterone propionate or methyl testosterone, these hormones apparently exert little effect on either the total circulating plasma protein or the concentration of albumin or globulin.¹⁵⁷ Relative hypoproteinemia occurring shortly after androgen administration suggests either accelerated formation of tissue protein derived from plasma protein or preferential synthesis of the tissue protein.¹⁵⁸

The relation of adrenal steroids to nitrogen metabolism is not clear. In general, the metabolic effect attending administration of that group of adrenocortical steroids having an oxygen in the C11 position may eventuate in negative nitrogen balance. It has been suggested that the negative balance represents heightened gluconeogenesis, a manifestation of increased protein catabolism,¹⁵⁹ or conversely, lowered protein synthesis, a manifestation of decreased protein anabolism.¹⁶⁰ It has also been suggested that adrenocortical hormone directly influences the conversion of tissue proteins to amino acids¹⁶¹ and enhances the rate of amino acid deamination¹⁶² and that the adrenal cortex elaborates a nitrogen-sparing factor. Impaired production of this factor may be responsible for the protracted biologic and metabolic abnormality following acute injury,¹⁶⁰ characterized as the so-called "alarm reaction" of Selye.¹⁶³ The negative nitrogen balance associated with impaired synthesis or protein depletion, or both, may eventually condition the occurrence of a clinical protein-deficiency state. Provision of a high protein intake during both the immediate catabolic and later convalescent phase following infection or injury minimizes this conditioned malnutrition.

The amino acids are usually obtained from dietary sources. Peptic, tryptic and enteric digestion of protein provides assimilable amino acids that are largely absorbed unchanged in the small intestine but may enter the circulation via thoracic-duct lymph. Absorbed amino acids are readily taken up by the tissues, particularly the liver.¹⁶⁴ Some amino acids serve as precursors or constituents of biologic substances, such as vitamins, co-enzymes, hormones and various detoxication products. Some are converted into tissue proteins. Others may be utilized for energy or contribute directly to the various non-protein nitrogen moieties. Some of the metabolic implications of the essential amino acids are given in Table 10.

The metabolism of the amino acids involves deamination (removal of the alpha-amino group), amination (the reverse of this procedure) and transamination (amination without participation of ammonia).¹⁷⁶ The energy derived from these metabolic reactions is reported to account for the elevated basal metabolic rate, or the so-called "specific dynamic action," following ingestion or infusion of proteins or amino acids.¹⁷⁷

- 1 Hegsted D M Tsongas A G, Abbott, D B, and Stare, F J Protein requirements of adults *J Lab & Clin Med* 31 261-284, 1946
- 2 Grossman C M, Sappington T S, Burrows B A, Lavietes, P H, and Peters J P Nitrogen metabolism in acute infections *J Clin Investigation* 24 523-531 1945
- 3 Peters J P Problems of nitrogen metabolism *Federation Proc* 3 197, 1944
- 34 Kenyon A T Knowlton K Sandford I Koch F C., and Lotwin G Comparative study of metabolic effects of testosterone propionate in normal men and women and in eunuchoidism. *Endocrinology* 26 26-45 1940
- 55 Kenyon A T Sandford I Bryan A H Knowlton K and Koch F C Effect of testosterone propionate on nitrogen electrolyte water and energy metabolism in eunuchoidism *Endocrinology* 23 135-153 1938
- 56 Albright F Parson W and Bloomberg E Cushing's syndrome interpreted as hyperadrenocorticism leading to hypergluconeogenesis results of treatment with testosterone propionate *J Clin Endocrinol* 1.375-384 1941
- 157 Abels J C Young N F and Taylor H C Jr Effects of testosterone and of testosterone propionate on protein formation in man *J Clin Endocrinol* 4 198-201 1944
- 158 Male sex hormones and protein metabolism *Nutrition Rev* 3.53, 1945
- 159 Long C N H Discussion of mechanism of action of adrenal cortical hormones on carbohydrate and protein metabolism *Endocrinology* 30 870-885 1942
- 160 Albright, F Cushing's syndrome its pathological physiology, its relationship to adreno-genital syndrome and its connection with problem of reaction of body to injurious agents ("alarm reaction of Selye). *The Harvey Lectures* (1942-1943) 38 123-186 1943
- 161 Long C N H, Katzin B and Fry E G Adrenal cortex and carbohydrate metabolism *Endocrinology* 26 309-344 1940
- 162 Ingle D J Physiological action of adrenal hormones In *The Chemistry and Physiology of the Hormones* Edited by F R Moulton 243 pp Washington D C. American Association for the Advancement of Science 1944
- 163 Selye H Studies on adaptation *Endocrinology* 21 169-188 1937
- 164 Van Slyke D D Physiology of amino acids *Science* 25 259 263, 1942
- 165 *The Chemistry of the Amino Acids and Proteins* Edited by C. L. A Schmidt. Second edition 1290 pp Springfield and Baltimore Charles C Thomas 1944
- 166 Butts J S Blunden, H, and Dunn M S Studies in amino acid metabolism III Fate of *dl* leucine *dl*-norleucine and *dl* isoleucine in normal animal *J Biol Chem* 120 289-295 1937
- 167 Hegsted D M Hay A L and Stare F J Chemical clinical and immunologic studies on products of human plasma fractionation XXIV Studies on nutritive value of human plasma fractions. *J Clin Investigation* 24 657-661 1945
- 168 Block R J and Bolling D *The Amino Acid Composition of Proteins and Foods Analytical methods and results* 396 pp Springfield and Baltimore Charles C Thomas 1945
- 169 Rose W C., and Eppstein S H Dietary indispensability of valine *J Biol Chem* 127 677-684 1939
- 170 Wells H G *Chemical Pathology* Second edition 616 pp Philadelphia W B Saunders Company 1914
- 171 Holt L E Jr Albanese A A Shettles L B Kajdi C and Wangerin D M Studies of experimental amino acid deficiency in man I Nitrogen balance *Federation Proc* 1 116 1942
- 172 Totter J R. and Day P L Cataract and other ocular changes resulting from tryptophane deficiency *J Nutrition* 24 159-166 1942
- 173 Levine S Z Marples E. and Gordon H H Defect in metabolism of aromatic amino acids in premature infants role of vitamin C *Science* 90 620 1939
- 174 Dann M Marples E. and Levine S Z Phenylpyruvic oligophrenia report of case in infant with quantitative chemical studies of urine *J Clin Investigation* 22 87-93 1943
- 175 MacCallum F O and Miles J A R Transmissible disease in rats inoculated with material from cases of infective hepatitis *Lancet* 1 35 1946
- 176 Cahill W M In *Outline of the Amino Acids and Proteins* Edited by M Sahyun 251 pp New York Reinhold Publishing Corporation 1944
- 177 Kriss M Specific dynamic effects of amino acids and their bearing on causes of specific dynamic effects of proteins *J Nutrition* 21 237-274 1941
- 178 Mitchell H H and Block R J Some relationships between amino acid contents of proteins and their nutritive values for rats *J Biol Chem* 163 599-620 1946
- 179 Olsen N S, Hemmingway A and Nier A O Metabolism of glycine I Studies with stable isotope of carbon *J Biol Chem* 148 611-618 1943
- 180 Pauling L Theory of structure and process of formation of antibodies *J Am Chem Soc* 62 2643 2657 1940
- 181 Heidelberger, M In *Outline of the Amino Acids and Proteins* Edited by M Sahyun 251 pp New York Reinhold Publishing Corporation 1944
- 182 Calvery H O Analysis of Type I pneumococcus specific precipitate *J Biol Chem* 112 167-169 1935

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALORY, MD, Editor

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CASE 33021

PRESENTATION OF CASE

A twenty-seven-year-old, single, unemployed man entered the hospital because of chronic diarrhea and weight loss

Five years before admission the patient had suddenly developed lower abdominal cramps and profuse watery diarrhea He was admitted to a hospital, where a diagnosis of chronic ulcerative colitis was confirmed by x-ray and sigmoidoscopic examinations Repeated search for parasites in the stools was negative, as were blood cultures and serologic tests After four weeks he was discharged essentially unimproved, having lost 30 pounds He remained at home on restricted activity, with persistent, nonbloody diarrhea (five or six movements daily) A year later an exacerbation sent him to

another hospital for three months By the time of discharge the diarrhea had subsided, and he had regained the weight lost He then worked as a taxi driver for six weeks before another exacerbation sent him home, where he remained a chronic and neglected invalid until a month before admission. At that time, with the onset of an upper respiratory infection, the diarrhea became worse, and the patient's general condition deteriorated rapidly Anorexia, edema, weakness and severe perianal inflammation developed The weight fell from 125 to 85 pounds

Physical examination disclosed a pale and emaciated patient with a moderate pitting edema up to the axilla He lay incontinent in bed, discharging semisolid stools frequently The skin was dry, shiny, tender and red over both femoral trochanters Severe inflammation with multiple draining abscesses surrounded the anus The tongue was abnormally reddened, with irregular patches of denudation of the epithelium The prepuce was edematous There was dullness over the right lung base, and the breath sounds were diminished The abdomen was tense but not tender The area of liver dullness extended 2 cm below the costal margin

The temperature was 98°F, the pulse 92, and the respirations 22 The blood pressure was 90 systolic, 60 diastolic

Examination of the blood revealed a red-cell count of 3,700,000, with a hemoglobin of 8 gm per 100 cc, and a white-cell count of 8500, with 66 per

amino acids — lysine, methionine, tryptophane, threonine and leucine and probably arginine — but is relatively low in tryptophane and isoleucine^{167, 178} Gamma globulin similarly contains at least these five essential amino acids with relatively large numbers of hydroxy-amino groups affording easily labile hydrogen bonds, beta globulin and fibrinogen include at least four of the essential amino acids, apparently lacking lysine

Many amino acids are intimately concerned with the metabolism of carbohydrate. There is some evidence that much of the carbohydrate formed after the administration of glycogenic amino acids such as glycine does not originate by direct conversion of the amino acid¹⁷⁹ but may depend on enzymatic conversion of some intermediary metabolite¹⁷⁶ Many of the vitamin B components involved in carbohydrate metabolism function as prosthetic groups of enzymes. Undoubtedly, specific amino acid complexes are necessary for the formation of the appropriate enzyme system

The relation of specific amino acids to some mechanisms of immunity is of considerable interest. It is thought that simple amino acids, as such, are not of primary significance in this regard. They are, however, indirectly involved as structural units in more complex proteins. According to Pauling's¹⁸⁰ theory of antibody formation, reactive antigen having a specific pattern penetrates to the sites of globulin formation and stimulates synthesis of specifically modified antibody globulin. The antibody globulin chain is modified, during synthesis, by coiling about the reactive antigen groups in such fashion as to template their configuration by surface approximation — thus achieving specificity¹⁸⁰. The spatial modification of the newly synthesized antibody globulin may owe its lability to the large number of easily converted hydrogen bonds contributed by hydroxy-amino acids, such as tyrosine, serine and threonine¹⁸¹. Threonine is an indispensable amino acid and must be supplied preformed in the diet. Tyrosine may be derived from phenylalanine, another essential amino acid. These amino acids are components of gamma globulin. Analyses of large quantities of several specific antigen-antibody precipitates have indicated an amino acid composition similar to that of typical serum globulin¹⁸². Application of isotopic analytic methods has demonstrated that protein antibody in actively immunized animals takes up dietary nitrogen in a manner similar to that of plasma globulin and other tissue proteins^{6, 7}. The available evidence, therefore, indicates that specific protein antibody synthesis is merely one phase of general protein synthesis and is at least partially dependent on adequate amino acid supply and metabolism.

SUMMARY

The application of newer experimental technics to problems of protein structure and function has

abetted clinical understanding of plasma protein significance. This paper attempts to correlate some of the recent data derived from physiologic, biochemical, physicochemical, nutritional, immunologic and clinical investigations in terms of their clinical implications.

REFERENCES

- 116 Wu H. Separate analyses of corpuscles and plasma. *J Biol Chem* 51:21-31, 1922.
- 117 Mackay, E. M. and MacKay, L. L. Concentration of urea in blood of normal individuals. *J Clin Investigation* 4:295-305, 1927.
- 118 Farr, L. E., McCarthy, W. C., and Francis, T. Jr. Plasma amino acid levels in health and in measles, scarlet fever and pneumonia. *Am J Med Sci* 203:668-673, 1942.
- 119 Schmidt, E. G. Amino-acid content of blood in health and in disease. *Arch Int Med* 44:351-361, 1929.
- 120 Lytle, J. D., Goettsch, E., Greenley, D. M., Grim, W. M., and Dunbar, P. Amino acid studies. II. Plasma amino acid retention as evidence of impaired liver function. Investigations in children with nephrosis and liver disease. *J Clin Investigation* 22:167-181, 1943.
- 121 Hamilton, P. B., and Van Slyke, D. D. Gasometric determination of free amino acids in blood filtrates by ninhydrin-carbon dioxide method. *J Biol Chem* 150:231-250, 1943.
- 122 Peters, J. P. Determination of creatinine and creatine in blood and urine with photoelectric colorimeter. *J Biol Chem* 146:179-185, 1942.
- 123 Tierney, N. A. and Peters, J. P. Mode of excretion of creatine and creatinine metabolism in thyroid disease. *J Clin Investigation* 22:595-602, 1943.
- 124 Jacobson, B. M. Uric acid in serum of gouty and of non-gouty individuals: its determination by Folin's recent method and its significance in diagnosis of gout. *Ann Int Med* 11:1277-1295, 1918.
- 125 Bollman, J. L., Mann, F. C., and Magath, T. B. Studies on physiology of liver. VIII. Effect of total removal of liver on formation of urea. *Am J Physiol* 69:371-392, 1924.
- 126 Krebs, H. A., and Henseleit, K. Z. Untersuchungen über die Harnstoffbildung im Tierkörper. *Ztschr f Physiol Chem* 210:33-65, 1932.
- 127 Leuthardt, F. Untersuchungen über die Harnstoffbildung aus Glutamin. *Ztschr f Physiol Chem* 252:238-260, 1938.
- 128 Bach, S. J. On mechanism of urea formation. *Biochem J* 33:1813-1844, 1939.
- 129 Shermis, D., and Rittenberg, D. Some interrelationships in general nitrogen metabolism. *J Biol Chem* 153:401-421, 1944.
- 130 Mosenthal, H. O., and Bruges, M. Urea ratio as measure of renal function. *Arch Int Med* 55:411-419, 1935.
- 131 Greenberg, D. M. In *Outline of the Amino Acids and Proteins*. Edited by M. Sahyun. 251 pp. New York: Reinhold Publishing Corporation, 1944.
- 132 Grossman, C. M. Effect of amino acids on serum and urine creatine. *J Clin Investigation* 24:380-383, 1945.
- 133 Hoffman, W. S., Kozoll, D. D., and Osgood, B. Blood chemical changes following intravenous administration of casein hydrolysate to human subjects. *Proc Soc Exper Biol & Med* 61:137-140, 1946.
- 134 Savers, M. A., Sayers, G., Engel, M. G., Engel, F. L., and Long, C. N. H. Elevation of plasma amino nitrogen as index of gravity of hemorrhagic shock. *Proc Soc Exper Biol & Med* 60:20-22, 1945.
- 135 Levenson, S. M., Adams, M. A., Green, R. W., Lund, C. C., and Taylor, F. H. L. Plasma alpha amino nitrogen levels in patients with thermal burns. *New Eng J Med* 235:467-471, 1946.
- 136 Bloch, K., and Schoenheimer, R. Biological precursors of creatine. *J Biol Chem* 138:167-194, 1941.
- 137 Borsook, H., and Dubnoff, J. W. Metabolism of proteins and amino acids. *Ann Rev Biochem* 12:183-204, 1943.
- 138 DuVigneaud, V., Cohn, M., Chandler, J. P., Schenck, J. R., and Simmonds, S. Utilization of methyl group of methionine in biological synthesis of choline and creatine. *J Biol Chem* 149:625-641, 1941.
- 139 Wilkins, L., and Fleischmann, W. Effects of thyroid on creatine metabolism with discussion of mechanism of storage and excretion of creatine bodies. *J Clin Investigation* 25:360-377, 1946.
- 140 Quick, A. J. In *Outline of the Amino Acids and Proteins*. Edited by M. Sahyun. 251 pp. New York: Reinhold Publishing Corporation, 1944.
- 141 Bauer, W., and Klemperer, F. Gout. Chap. 12. In *Diseases of Metabolism*. Edited by G. F. Duncan. 985 pp. Philadelphia: W. B. Saunders Company, 1942. Pp. 609-654.
- 142 Talbot, J. H. Gout. Reprinted from *Oxford Loose Leaf Medicine*. Pp. 79-134. New York: Oxford University Press, 1943.
- 143 Gamble, J. L. *Chemical Anatomy: Physiology, and Pathology of Extracellular Fluid*. Department of Pediatrics, Harvard Medical School, 1942.
- 144 Schiff, L., and Stevens, R. J. Elevation of urea nitrogen content of blood following hematemesis or melena. *Arch Int Med* 64:1239-1251, 1939.
- 145 Chunn, C. F., Harkins, H. N., and Boals, R. T. Alimentary azotemia and bleeding peptic ulcer syndrome. *Arch Surg* 43:773-778, 1941.
- 146 Greenblatt, I. J., and Cohn, T. D. Azotemia in gastro-intestinal bleeding: ingestion of shed blood in humans. *Am J Med Sci* 211:565-570, 1946.
- 147 Haden, R. L., and Orr, T. G. Excretion of nitrogen after upper gastrointestinal tract obstruction. *J Exper Med* 45:433-436, 1927.
- 148 Borsook, H., and Keighley, G. L. "Continuing" metabolism of nitrogen in animals. *Proc Roy Soc London* 118:488, 1935.
- 149 Osborne, T. B., and Mendel, L. B. Amino acids in nutrition and growth. *J Biol Chem* 17:325-349, 1914.
- 150 Macy, I. G. *Nutrition and Chemical Growth in Childhood*. Vol. 1. Evaluation. 432 pp. Springfield: Charles C. Thomas, 1942.

1. Hearsted D M., Tsongas, A G., Abbott, D B., and Stare F J Protein requirements of adults *J Lab & Clin Med* 31 261-284, 1946
2. Grossman C M Sappington T S., Burrows B A., Lavieter, P H., and Peters J P Nitrogen metabolism in acute infections *J Clin Investigation* 24:523-531 1945
3. Peters J P Problems of nitrogen metabolism *Federation Proc* 3 197 1944
4. Kenyon A T Knowlton K Sandiford I Koch F C. and Lotwin G Comparative study of metabolic effects of testosterone propionate in normal men and women and in eunuchoidism. *Endocrinology* 26 26-45 1940
5. Kenyon A T Sandiford I Bryan A H Knowlton K. and Koch F C. Effect of testosterone propionate on nitrogen electrolyte water and energy metabolism in eunuchoidism. *Endocrinology* 23 135-153 1938
6. Albright F Parson W and Bloomberg E Cushing's syndrome interpreted as hyperadrenocorticism leading to hyperglucocorticogenesis results of treatment with testosterone propionate *J Clin Endocrinol* 1 375-384 1941
7. Abe's J C Young N F and Taylor H C Jr Effects of testosterone and of testosterone propionate on protein formation in man *J Clin Endocrinol* 4 198-201 1944
8. Male sex hormones and protein metabolism *Nutrition Rev* 3:55 1945
9. Long C N H Discussion of mechanism of action of adrenal cortical hormones on carbohydrate and protein metabolism. *Endocrinology* 30 870-88, 1942
10. Albright, F Cushing's syndrome its pathological physiology its relationship to adreno-genital syndrome and its connection with problem of reaction of body to injurious agents ('alarm reaction of Selye') *The Harvey Lectures* (1942-1943) 38 123 186 1943
11. Long C N H., Katzin B., and Fry E G Adrenal cortex and carbohydrate metabolism. *Endocrinology* 26:309-344 1940
12. Ingle D J Physiological action of adrenal hormones. In *The Chemistry and Physiology of the Hormones* Edited by F R Moulton 243 pp Washington D.C. American Association for the Advancement of Science, 1944
13. Selye H Studies on adaptation. *Endocrinology* 21 169-188 1937
14. Van Slyke, D D Physiology of amino acids *Science* 25 259-263 1942
15. *The Chemistry of the Amino Acids and Proteins* Edited by C. L. A Schmidt. Second edition 1290 pp Springfield and Baltimore Charles C Thomas 1944
16. Butts J S Blunden H and Dunn, M S Studies in amino acid metabolism. III Fate of *dl*-leucine *dl* norleucine, and *dl*-isoleucine in normal animal *J Biol Chem* 120 289-295 1937
167. Hegsted D M Hay A L. and Stare F J Chemical clinical and immunologic studies on products of human plasma fractionation XXIV Studies on nutritive value of human plasma fractions. *J Clin Investigation* 24 657-661 1945
168. Block, R. J. and Bolling D *The Amino Acid Composition of Proteins and Foods Analytical methods and results* 396 pp Springfield and Baltimore Charles C Thomas 1945
169. Rose W C. and Eppstein S H Dietary indispensability of valine *J Biol Chem* 127 677-684 1939
170. Wells H G *Chemical Pathology* Second edition 616 pp Philadelphia W B Saunders Company 1914
171. Holt L E Jr Albanese, A A Shettles L B Kajdi C and Wangerin D M Studies of experimental amino acid deficiency in man I Nitrogen balance *Federation Proc* 1 116 1942
172. Totter J R. and Day P L Cataract and other ocular changes resulting from tryptophane deficiency *J Nutrition* 24 159-166 1942
173. Levine S Z Marples E. and Gordon H H Defect in metabolism of aromatic amino acids in premature infants role of vitamin C *Science* 90 620 1939
174. Dann M Marples E., and Levine S Z Phenylpyruvic oligophrenia report of case in infant with quantitative chemical studies of urine *J Clin Investigation* 22 87 95 1943
175. MacCallum F O and Miles J A R Transmissible disease in rats inoculated with material from cases of infective hepatitis *Lancet* 1 3-5 1946
176. Cahill W M In *Outline of the Amino Acids and Proteins* Edited by M Sahyun 251 pp New York Reinhold Publishing Corporation 1944
177. Kriss M Specific dynamic effects of amino acids and their bearing on causes of specific dynamic effects of proteins *J Nutrition* 21 257 274 1941
178. Mitchell H H. and Block R. J Some relationships between amino acid contents of proteins and their nutritive values for rats *J Biol Chem* 163 599-620 1946
179. Olsen N S, Hemmingway A. and Nier A O Metabolism of glycine I Studies with stable isotope of carbon *J Biol Chem* 148 611-618 1943
180. Pauling L Theory of structure and process of formation of antibodies *J Am Chem Soc* 62 2643 2657 1940
181. Heidelberger M In *Outline of the Amino Acids and Proteins* Edited by M Sahyun 251 pp New York Reinhold Publishing Corporation 1944
182. Calvery H O Analysis of Type I pneumococcus specific precipitate *J Biol Chem* 112 167-169, 1935

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

CASE 33021

PRESENTATION OF CASE

A twenty-seven-year-old, single, unemployed man entered the hospital because of chronic diarrhea and weight loss.

Five years before admission the patient had suddenly developed lower abdominal cramps and profuse watery diarrhea. He was admitted to a hospital, where a diagnosis of chronic ulcerative colitis was confirmed by x-ray and sigmoidoscopic examinations. Repeated search for parasites in the stools was negative, as were blood cultures and serologic tests. After four weeks he was discharged essentially unimproved, having lost 30 pounds. He remained at home on restricted activity, with persistent, nonbloody diarrhea (five or six movements daily). A year later an exacerbation sent him to

another hospital for three months. By the time of discharge the diarrhea had subsided, and he had regained the weight lost. He then worked as a taxi driver for six weeks before another exacerbation sent him home, where he remained a chronic and neglected invalid until a month before admission. At that time, with the onset of an upper respiratory infection, the diarrhea became worse, and the patient's general condition deteriorated rapidly. Anorexia, edema, weakness and severe perianal inflammation developed. The weight fell from 125 to 85 pounds.

Physical examination disclosed a pale and emaciated patient with a moderate pitting edema up to the axilla. He lay incontinent in bed, discharging semisolid stools frequently. The skin was dry, shiny, tender and red over both femoral trochanters. Severe inflammation with multiple draining abscesses surrounded the anus. The tongue was abnormally reddened, with irregular patches of denudation of the epithelium. The prepuce was edematous. There was dullness over the right lung base, and the breath sounds were diminished. The abdomen was tense but not tender. The area of liver dullness extended 2 cm below the costal margin.

The temperature was 98°F, the pulse 92, and the respirations 22. The blood pressure was 90 systolic, 60 diastolic.

Examination of the blood revealed a red-cell count of 3,700,000, with a hemoglobin of 8 gm per 100 cc, and a white-cell count of 8500, with 66 per

cent neutrophils. The urine had a specific gravity of 1.026, with occasional white cells in the sediment, and examination was negative for albumin, sugar, red cells and casts. Guaiac tests on the stools were strongly positive. The total serum protein was 3.67 gm, and the nonprotein nitrogen 22 mg per 100 cc, the sodium was 140.3 milliequiv, and the chloride 102 milliequiv per liter. An x-ray film of the chest showed a small amount of fluid on each side, with a few linear areas of density in the lingula of the left upper lobe.

In the hospital the patient's condition was consistently unsatisfactory. On the fourth hospital day massive swelling of the scrotum, penis and legs had developed, along with generalized itching and a pink papular rash on the abdomen and legs, the administration of 3 gm of sulfadiazine daily was begun. A single whole-blood transfusion was given each day for five days, and the hemoglobin increased to 12 gm per 100 cc. After the fifth transfusion the patient suffered a chill, and the temperature rose to 100.8°F. Within the next twenty-four hours the urinary output fell from a former level of 1750 cc to 750 cc, it remained low for several days, gradually returning to a level of 2250 cc by the fourteenth day. The urine gave a + test for albumin on the fourth day and a ++++ test on the ninth. Thereafter, the test was +++ to ++++, the reaction was acid, and the specific gravity was between 1.004 and 1.014. The sediment on numerous occasions had 5 or 6 white cells, occasional red cells and 0 to many hyaline casts per high-power field.

Doses of 200 cc of human serum albumin were given daily for nearly two weeks. The total protein rose from 3.67 to 4.42 gm per 100 cc, with an albumin-globulin ratio of 1.56. Other treatment consisted of vitamins, 10 per cent Amigen, dextrose in water and courses of sulfapyridine and, later, penicillin. The diarrhea persisted. For many days the patient was markedly edematous despite the daily output of 2000 to 2500 cc of urine, which contained from 23 to 45 gm of protein on numerous determinations. He had satisfactory diuresis only after the administration of acacia, a total of 150 gm having been given. The temperature ranged between 99 and 101°F.

X-ray examinations of the chest continued to show small to moderate amounts of fluid, with occasional areas of density and haziness suggesting consolidation or multiple infarcts. Toward the end of the second hospital week the abdomen became diffusely tender and remained so for several days.

During the first month the serum protein level was usually about 4 gm, and the nonprotein nitrogen 20 to 24 mg per 100 cc. A phenolsulfonephthalein test on the twenty-fifth day showed 25 per cent excretion of the dye in thirty minutes and 60 per cent in two hours. A Congo-red test at about that time showed 33 per cent retention of the dye in the serum.

Mercupurin was given after the supply of serum albumin ran out. The edema gradually diminished and the temperature approached normal, but the patient remained extremely ill. The sinuses about the anus continued to drain. On the forty-fifth hospital day an ileostomy was performed. Post-operatively intractable small-bowel distention developed. The urine output fell to 200 cc over a seven-day period, and the nonprotein nitrogen rose to 150 mg per 100 cc. The insertion of a Miller-Abbott tube failed to improve the distention. The chloride fell to 76 milliequiv per liter. Terminally there was anuria for thirty-six hours. Hyperpnea and involuntary movements developed, and death occurred on the fifty-fourth hospital day.

DIFFERENTIAL DIAGNOSIS

DR MARIAN W. ROPES: In this patient there were surely two major sites of disease—the gastrointestinal tract and the genitourinary tract. As I see it, the problem is to decide the nature of the two diseases, whether they were interrelated and, if so, in what manner. So far as the gastrointestinal disease is concerned, the history, in general, is consistent with that of chronic idiopathic ulcerative colitis. Unfortunately we are not told anything about the results of proctoscopic or x-ray studies, but we are told that they were consistent with this disease at least during the first attack. It would be of interest to know if these studies were repeated during the second attack and, if so, what the findings were.

DR HAROLD E. ELRICK: Barium-enema and proctoscopic examinations were not done.

DR ROPES: I assume that the findings in the first attack corroborated the diagnosis and that the findings in the terminal attack were similar. There are some unusual features, however. The degree of perianal inflammation with many draining abscesses is unusual, this is not inconsistent with the diagnosis, however, and does not make it necessary for us to consider seriously other possible causes of ulcerative colitis, such as tuberculosis. The degree of edema seems definitely more than one would expect in such a patient with ulcerative colitis, particularly since the edema apparently persisted and possibly increased, although it is difficult to be sure of that, since the serum protein rose to 4.5 gm per 100 cc. If the edema had been on a purely nutritional basis it would have been unusual for it to fail to respond to the administration of albumin, with its resulting elevation of the serum protein, and subsequently to respond to acacia. In addition, the pulmonary changes were not characteristic.

May we see the x-ray films?

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DR ROPES The fluid in the pleural cavities is consistent with a generalized anasarca. The small areas of consolidation varying from time to time are difficult to interpret, I think that they were not specifically related to the underlying gastrointestinal or genitourinary disease. The changes in the skin and tongue were in general consistent with the nutritional disturbance. That is not true of the rash, and I find no explanation for the itching and rash, which were probably associated, other than the possibility of some medication that we do not know about. Clubbing of the fingers, I judge, was not recent. I should have thought that it would have been seen after five years of ulcerative colitis.

DR ELRICK It was present.

DR ROPES Apparently, there were no joint symptoms, which might have been expected, since joint involvement is not too rare in ulcerative colitis. The abdominal tenderness in the second week is consistent with the degree of tenderness seen in uncomplicated ulcerative colitis, but the suddenness of onset suggests the possibility of a small perforation, which I consider unlikely, however. Similarly, the ileus, with the small-bowel obstruction and distention that occurred following operation, could have been secondary to the disease itself but suggests the possibility of superimposed peritonitis. In general, therefore, the gastrointestinal involvement is consistent with chronic ulcerative colitis — but not the genitourinary involvement.

Several possibilities should be considered regarding the genitourinary difficulties. As I have said, the degree of edema was out of proportion to what one would expect in a patient with ulcerative colitis at that stage. It suggests a nephrotic state. There is little evidence that this could have been the nephrotic state of chronic nephritis, although it is impossible to rule out nephritis. The onset of the acute illness following a respiratory infection and the sudden downhill course suggest that diagnosis, but the findings are somewhat against it. On the other hand, the urinary findings, with the high albumin in the absence of cells and the presence of only a few or a moderate number of casts, the nephrotic picture, the low nonprotein nitrogen until the terminal stage and the relatively good phenol-sulfonephthalein excretion are typical of amyloid disease of the kidney.

Another possibility to be considered is whether or not sulfonamide treatment or transfusion reaction caused any of the renal damage in this patient, as suggested by the few signs of renal involvement at the time of admission and the marked changes after sulfonamide treatment had been started and after the transfusion reaction. On the other hand, such marked changes without elevation of the nonprotein nitrogen lasting for a long period are unusual in kidney damage due to either of these factors alone. Therefore, I think that amyloid involvement of the kidney is the most probable explanation of the

renal disease. If so, it is interesting, because such involvement in ulcerative colitis is, I think, extremely rare. I know of only one case in the literature — that reported by Moschowitz,* ten years ago. The serum globulin, which is frequently high in the diseases to which amyloid is secondary, was definitely low in this patient — below 2 gm per 100 cc. The liver enlargement is consistent with amyloid disease but is not greater than what one would expect with ulcerative colitis of this severity. If amyloid disease caused the renal involvement, the question arises whether sulfonamide treatment or a transfusion reaction hastened the renal failure. I think that this is impossible to answer clinically. I have been impressed, however, with the course of two patients with amyloid disease of the kidney who died here fairly recently. Both went rapidly into renal failure with marked urinary changes, and in both sulfonamides or penicillin had been given before the changes occurred. I have no idea whether or not the sulfonamide treatment or transfusion reaction was related to the renal failure in this patient.

If this patient had amyloidosis secondary to ulcerative colitis, it is of interest that amyloidosis is not a rare complication of rheumatoid arthritis and that rheumatoid arthritis is often associated with ulcerative colitis. In the hospital at the present time we have a woman with probable rheumatoid arthritis, acute ulcerative colitis and amyloid disease.

In putting this picture together, therefore, I shall conclude that this patient had chronic idiopathic ulcerative colitis, with secondary amyloid disease involving at least the kidneys. Whether the liver was also involved, I do not know, although it is probable that it was. I do not know whether the sulfonamide treatment or transfusion reaction further damaged a kidney in which amyloid disease was already present.

DR JOSEPH C AUB Would Dr Ropes like to suggest that this man had amyloid disease of the small intestine?

DR ROPES We have had a great deal of discussion regarding whether or not amyloid disease gives active clinical disease of the gastrointestinal tract. There is no question that amyloid can be deposited in the gastrointestinal tract. The clinical symptoms arising from this amyloid involvement are apparently rare. We have a patient in the hospital with amyloidosis and small polypoid masses in the lower gastrointestinal tract, one of which has been biopsied. I do not know the result.

DR AUB I have seen amyloid disease with involvement of the whole small intestine.

DR ROPES With symptoms?

DR AUB I cannot remember.

DR CHARLES H BURNETT We were perplexed in the same way about the renal situation and the

*Moschowitz E. Clinical aspects of amyloidosis. *Ann Int Med* 10: 3-85 1936.

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DR TRACY B. MALLORY: The X-ray Department sent the report over that there was no point in showing the films, which add nothing to what is given in the record.

ak, noted palpitation and found it difficult to breathe. There was a sense of substernal oppression but no pain. A physician found a blood pressure of 230 systolic, 140 diastolic, albuminuria and glycosuria. The face was swollen. The patient remained in bed for twelve days with orthopnea and severe generalized abdominal pain, he also had a severe frontal headache, dizziness and black spots before the eyes. Vague pains and numbness on the dorsal surfaces of the feet and in the right shoulder were observed at the same time. These symptoms, which persisted and increased during the succeeding months, constituted the chief complaint on admission. Four and a half months before admission the patient was admitted to another hospital. Albuminuria was marked, the fasting blood sugar was 70 mg per 100 cc. The nonprotein nitrogen was normal, and an intravenous pyelogram showed 34 per cent excretion of the dye in one hour. Red and white cells were found in the urinary sediment. The patient was discharged in ten days still not improved. There were persistent hematuria and a weight loss of 14 pounds. He was taking 14 units of protamine zinc insulin daily. Two weeks later he felt sufficiently improved to go back to work. Blurring of vision and pain in the feet and shoulders persisted. Two and a half months later follow-up examination at the same hospital showed the blood pressure to be 194 systolic, 78 diastolic, and the nonprotein nitrogen to be 74 mg per 100 cc. Thereafter he was followed in the Out Patient Department of this hospital, where the blood sugar levels were found to be 135, 149 and 258 mg per 100 cc on different occasions. There were a moderate anemia and a moderate leukocytosis, as well as a carbon dioxide combining power between 23.5 and 25.8 milliequiv per liter.

Physical examination on entry showed an apical systolic murmur, the aortic second sound was louder than the pulmonic. The blood pressure was 172 systolic, 98 diastolic. There were small hemorrhages in both fundi, and a few whitish exudates were seen. The lungs were normal. Pulsations were felt in all the main arteries of the lower extremities, and oscillographic abnormalities were minimal. Neurologic examination showed only a slight decrease in vibration and position sense in the lower extremities. The knee and ankle jerks were hyperactive but equal.

Examination of the blood revealed a red-cell count of 3,300,000, with a hemoglobin of 70 per cent. The urine gave a ++ test for albumin. The urinary sediment contained occasional white cells and 4 or 5 red cells per high-power field, with rare hyaline and finely granular casts. Cultures of the urine showed no growth. The phenolsulfonephthalein test showed 17 per cent excretion of the dye in one hour and 24 per cent excretion in two hours. The nonprotein nitrogen was 66 mg, and the fasting blood sugar 135 mg per 100 cc. The urine sugar reactions were consistently green. Plain films of the abdomen

showed the kidney outlines to be indistinct, the left kidney appeared normal, and the right was not definitely visible. On an x-ray film of the chest the heart did not appear definitely enlarged. Films of the feet showed slight calcification of the dorsalis pedis arteries. An electrocardiogram taken shortly after admission demonstrated slightly sagging ST segments in Leads 1, 2 and 3, a depressed ST₄, and a sharply diphasic T₄. The rhythm was normal.

Treatment consisted of warm foot baths, massage and exercises. The pain and numbness in the lower extremities rapidly disappeared. On the fourth and sixth days the urine contained many red cells, but there was no other outward incident in the twelve-day hospital stay.

Final admission (six years later) After discharge the patient was followed in the diabetic clinic, where the blood sugar was normal and glycosuria was absent. He was taking 16 units of protamine zinc insulin daily and was following his diet. On the last visit to the clinic, five years before admission, the nonprotein nitrogen was 38 mg per 100 cc. The patient was fairly well until a year before admission, when he began to notice severe progressive weakness, dyspnea and failing vision. He was given digitalis by a physician, but the symptoms continued. He also suffered from urinary difficulty with nocturia and frequency. For several weeks before admission he had been confined to bed. Five days before admission he developed an epistaxis, which persisted and brought him to the Emergency Ward.

Physical examination showed an emaciated, pale and weak man who was bleeding profusely from the right nostril and gagging from blood clots in the nasopharynx. During the examination he vomited 60 cc of clotted blood. The pupils were small, but reacted to light and accommodation. The neck veins were distended, and the heart enlarged, extending 10 cm to the left of the midsternal line in the sixth interspace. There were no murmurs. There were rales at the bases of both lungs. The liver edge was palpable 4 cm below the costal margin. The bladder was felt 4 cm above the symphysis. There was thickening of the epididymis. The prostate was symmetrically enlarged and indurated. There was moderate pitting edema of the ankles and legs.

The temperature was 98.8°F, the pulse 105, and the respirations 20. The blood pressure was 160 systolic, 90 diastolic.

Examination of the blood revealed a red-cell count of 2,050,000, with a hemoglobin of 7 gm, and a white-cell count of 12,300, with 90 per cent neutrophils. The specific gravity of the urine was 1.004. The sugar reaction was green. On admission there was no albumin, but on the next day there was a ++++ test for albumin. The sediment was reported to contain innumerable bacteria.

The bleeding was stopped shortly after entry, and a whole-blood transfusion was administered. Two

sudden appearance of the nephrosis. A single examination of the urine was negative on admission, with the subsequent appearance of albuminuria following the administration of sulfonamides and blood. There was no evidence of a hemolytic reaction. And although a transfusion reaction was ruled out, we did not know what the influence of the sulfonamides was. We were strongly enough impressed to stop the sulfonamides, however.

DR ROPES: I neglected to mention the Congo-red test, which I thought was confirmatory evidence of amyloidosis. Retention of 67 per cent of the dye in the tissues, leaving only 33 per cent in the serum, is certainly presumptive evidence of the presence of amyloid.

DR BEVERLY TOWERY: Is there any evidence that Amigen or acacia influences amyloid disease?

DR ROPES: I do not know whether acacia does, but the repeated injection of sodium caseinate is one of the best ways of producing the disease experimentally in animals.

CLINICAL DIAGNOSES

Chronic ulcerative colitis

Nephrotic syndrome

Amyloid nephrosis?

Postoperative ileus

DR ROPES'S DIAGNOSIS

Chronic idiopathic ulcerative colitis, with secondary amyloidosis

ANATOMICAL DIAGNOSES

Ulcerative colitis

Amyloid degeneration of kidneys, liver, spleen and adrenal glands

Operation ileostomy, recent

Pulmonary embolus, with infarction of lung, small

Organizing thrombus of both common iliac arteries and inferior vena cava

PATHOLOGICAL DISCUSSION

DR MALLORY: At autopsy the peritoneal cavity was perfectly clean. There had been no peritonitis or mechanical obstruction following the ileostomy, and the dilatation of the small bowel must have been of a reflex origin. The entire large bowel was involved in a severe ulcerative process. The mucosa was markedly atrophied but showed an occasional bridge of mucosa across an area of ulceration. There was no ulcerative process in the ileum. Although the wall of the terminal segment of the ileum was edematous and thickened, it showed no amyloid. The liver was large, weighing 2500 gm, and was somewhat pale but not yellow or greasy and, we thought, not significantly fatty on gross examination, it was firmer than normal, and the markings were unusually prominent. We suspected amyloid, which was borne out by the histologic examination — in fact, there was rather extensive involvement in the liver. The spleen was large and showed typical

sago bodies characteristic of amyloid deposits in the malpighian corpuscles. The kidneys were markedly swollen, their combined weight being 600 gm, the cortex was extremely pale and thickened to 9 or 10 mm.

DR WADE VOLWILER: Did the acacia still remain in the organs?

DR MALLORY: It is not easy to see, I could not pick it out. The kidneys, as far as I could determine, represented a pure amyloid nephrosis. There were only moderate deposits of amyloid in the glomeruli but marked secondary degeneration of the tubules, especially the proximal convoluted tubules, as well as markedly dilated lumens containing a great deal of precipitated protein and much swollen epithelium. There was nothing to suggest a hemoglobinuric nephrosis or, so far as I could see, sulfonamide reaction.

There was a small pulmonary embolus, with a corresponding area of infarction, in the right lower lobe. The source of the embolus was a large thrombus that had almost completely occluded the lower 15 cm of the inferior vena cava and both common iliac veins.

As Dr Ropes pointed out, amyloid is an unusual complication of ulcerative colitis. I cannot remember having seen it before.

DR AUB: Was there any amyloid in the small intestine?

DR MALLORY: No, there was, however, severe amyloid disease of the adrenal glands — enough to make me wonder if the patient had had adrenal insufficiency.

A PHYSICIAN: Were anaerobic cultures made of the fluid draining from the anal sinuses?

DR MALLORY: No effort was made to culture the pus. Such sinuses are not a rare complication of idiopathic ulcerative colitis. They sometimes extend quite a distance on either side of the anus. We have seen cases in which both buttocks were almost completely destroyed.

CASE 33022

PRESENTATION OF CASE

First admission. A sixty-three-year-old postal clerk entered the hospital because of pain and numbness of the feet and shoulders.

Fourteen years before admission the patient was found to have had glycosuria without hyperglycemia. Two years later he entered a hospital because of hematuria. Diagnoses of diabetes mellitus and ureteral stone were made, and a right ureterolithotomy was performed. At the time of discharge the blood sugar was normal, and there was no glycosuria. For the following twelve years the patient was well. He took no insulin and ignored his diet. Five months before admission, on the way home from work, he became dizzy, felt tired and

In addition, the patient had diabetes and hypertensive heart disease, with cardiac enlargement and failure

DR JACOB LERMAN How do you explain the electrocardiographic findings unless he was taking digitalis or had a coronary infarct?

DR SHORT I am not an electrocardiographer, but believe that this patient's tracing was not specific for coronary disease, it may have been compatible with hypertension or myocardial disease and could have followed the administration of digitalis

CLINICAL DIAGNOSES

Hypertensive heart failure

Uremia

Diabetes mellitus

DR SHORT'S DIAGNOSES

Chronic pyelonephritis

Diabetes

Hypertensive heart disease, with cardiac enlargement and failure

ANATOMICAL DIAGNOSES

Chronic glomerulonephritis, inactive

Cardiac hypertrophy

Coronary sclerosis

Chronic passive congestion

Benign hyperplasia of prostate

(Diabetes mellitus)

PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY It is always a difficult clinical problem to decide what type of renal insufficiency will be found in a case of this sort. Sometimes, it is equally difficult or even quite impossible after one has seen the results of post-mortem examination. Dr Short decided to rule out intercapillary glomerulosclerosis—the Kimmelstiel-Wilson syndrome*—and was correct in so doing. A small number of glomeruli in the kidney showed slightly suggestive changes, but no more than one might find in any diabetic patient. That certainly was not the major cause of the trouble. The kidneys were markedly contracted, their combined weight being

only 100 gm. The surface was pitted and scarred, and the cortex was reduced to 2 mm in thickness. On microscopic examination the outstanding phenomenon was that almost every glomerulus was surrounded by a crescent of collagen that lay within and obliterated Bowman's capsule. I do not see how this could have been produced except by a capsular glomerulonephritis. The epithelial cells lining the capsule first proliferate and later give way to fibroblasts which lay down collagen. I am therefore quite content in this case to commit myself to a diagnosis of old chronic glomerulonephritis. I think that it is still within the limit of possibility that other pathologists would interpret this case differently. The patient had the basis for a pyelonephritis in the form of a hypertrophied prostate, cystitis, dilatation of the ureters and slight dilatation of the pelvis of the kidneys.

The heart was enlarged, presumably secondarily to the hypertension. The coronary arteries were markedly sclerotic and narrow but not occluded at any point. The myocardium, particularly the interventricular septum, showed slight patchy discoloration on gross examination and slight focal degeneration on microscopic examination. There was not, however, any significant area of infarction. The lungs and the liver both showed severe chronic passive congestion.

In a case of chronic renal insufficiency we always look with interest at the parathyroid glands. The first person who searched for them in this case did not find them, which I think is evidence that they were not markedly enlarged. Dr Castleman made a secondary search and found two glands of normal size and a tumor nodule measuring 1.0 by 1.5 cm. This turned out to be an interesting curiosity. The sections showed the characteristic picture of a fetal lung, with well formed bronchi and alveolar spaces lined with cuboidal epithelium. This is an infrequent but not extremely rare congenital anomaly. One hardly expects to find it in a seventy-year-old man, however, or as high in the neck as this one was. When bronchial buds grow into extrapleural tissues a small growth of lung tissue may occur, but since the lesion is extrapleural, it never expands and maintains the character of a fetal lung. In this case it was a coincidental lesion of purely pathological interest.

*Kimmelstiel, P., and Wilson, C. Intercapillary lesions in glomeruli of kidney. *Am. J. Path.* 12: 83-98, 1936.

days later the nonprotein nitrogen was 70 mg, and the fasting blood sugar 132 mg per 100 cc. The carbon dioxide combining power was 27.1 milliequiv per liter. The chloride was 106 milliequiv per liter, and the total protein 6.4 gm per 100 cc.

The nonprotein nitrogen level doubled in two days, reaching 145 mg per 100 cc, whereas the carbon dioxide dropped to 25 milliequiv per liter. The patient became comatose and died on the fourth hospital day.

DIFFERENTIAL DIAGNOSIS

DR CHARLES L. SHORT: In the first place, we must assume that this patient had diabetes on the basis of the history and the laboratory findings. This diagnosis was first made eighteen years before final admission, but he was under treatment for only six years. The diabetes was complicated at one point by neuritis, which was symptomatically relieved by therapy, and eye-ground changes consistent with diabetic retinopathy. The patient died in cardiac failure, the heart disease evidently being secondary to the long-standing high blood pressure. The episode five months before the first admission, when he suddenly developed weakness, dyspnea and palpitation, suggests a coronary occlusion, although he did not have actual pain. The clinical picture, however, and the electrocardiogram do not seem characteristic of that condition.

The real problem, it seems to me, is to determine the nature of the renal lesion. We might briefly recapitulate the course of the kidney disease at this point. Eighteen years before admission the patient had hematuria and a right ureteral calculus was removed, but no note is made of the blood pressure at that time. About twelve years later, he was found to have albuminuria and severe hypertension, so that there is no clue regarding whether the hypertension preceded the renal disease or vice versa. At the time of the first admission, red cells and casts were found in the urinary sediment, and nitrogen retention had already been noted. X-ray studies disclosed a left kidney that seemed to be of normal size, but the right kidney was not visible. Since the x-ray films are not here, I shall assume that they add nothing to the written report. I do not believe that we can draw any conclusion from the failure to see the right kidney, it may simply have been obscured. At that time the patient again showed marked hematuria, he was apparently well for five years, and the kidneys regained adequate function, since the nonprotein nitrogen was normal. A year before death he developed cardiac failure and finally uremia, which presumably accounted for the anemia and bleeding. At the final admission he continued to have albuminuria, and the sediment for the first time contained many bacteria.

A number of types of Bright's disease can produce a terminal picture of hypertension and uremia. I do not need to list them all, but I shall mention some

of them in the differential diagnosis. Since this patient was diabetic, one thinks of the renal lesion associated with diabetes — namely, intercapillary glomerulosclerosis. It would be hazardous to say that this condition was not found to some extent histologically in this patient, since certain authors report its presence, to some degree, in at least half the diabetic patients at autopsy. Slight glomerulosclerosis may also be found in nondiabetic patients. I hope that Dr. Mallory will comment on this point later. We are trying to determine the important cause for the renal failure, and I am therefore going to discard this condition as having been primarily responsible, chiefly because at no time did the patient present the nephrotic picture that is often associated with severe degrees of intercapillary glomerulosclerosis. The fact that he once had swelling of the face may represent renal edema, but I do not believe that we are justified in making this diagnosis merely because the patient was diabetic. Swelling of the face is suggestive of glomerulonephritis, but there was no definite history of an acute attack, so that we have no knowledge that the kidney disease preceded the hypertension. Nephrosclerosis or vascular nephritis is probably as good a bet as any, and in any event autopsy probably showed arteriolar changes in the kidneys in view of the long-standing hypertension. As a fundamental cause of the renal insufficiency, however, I am more in favor of a condition that has been recognized accurately only in recent years as an important cause of kidney disease and hypertension. I refer to pyelonephritis, which, in a chronic or healed stage, may result in the terminal picture shown by this patient. The ureteral calculus eighteen years before death may have been highly significant, either as a primary cause of obstruction and infection or on the basis of a preceding infection. It is true that the patient gave no history of an acute pyelonephritis, but such a history is not elicited in most cases. The urinary sediment showed no definite evidence of infection until just before death. Cultures at the first admission were negative, but the process may have been relatively quiescent or healed at that time. The hematuria, which may also have been due to recurrent urinary calculi, is sometimes prominent in this form of nephritis. Pyelograms at the first admission would have been helpful and perhaps diagnostic, although cases of pyelonephritis have been reported with negative x-ray findings. The fluctuation in the course of the disease and the return of adequate function after uremia had set in are compatible with pyelonephritis. At the final admission the nocturia and frequency, the urinary picture, the prostatic hypertrophy and the enlargement of the bladder suggest that another factor was involved in the last part of the illness — namely, an obstructing prostate with infection behind it. I realize that this is a somewhat slender chain of evidence, but chronic or healed pyelonephritis is my first choice.

laborative study by members of the New York Department of Health and by Drs Heubner and Armstrong of the National Institute of Health is undertaken.

At the National Institute of Health, an organism was isolated that possessed the morphologic, cultural and staining characteristics of the rickettsias. This organism was recovered from the tissues of a guinea mouse, which had been inoculated with blood drawn on the second day of fever from one of the patients. It produced illness in mice and guinea pigs and grew well in the yolk-sacs of fertile eggs. Further extract yolk-sac antigens were then prepared, and these were shown to fix complement when mixed with serums drawn from convalescent cases. This complement-fixation reaction was apparently specific so far as it was tested, except for cross reactions with serums from patients with Rocky Mountain spotted fever.

The agent was also isolated from a saline suspension of tissues of mites (*Allodermomyssus sanguineus*) collected in the house of the patient from whose blood the original rickettsia was obtained⁵ and a similar rickettsia was recovered from a mouse that was bitten by one of these mites. The strains isolated from the mite and from the mouse were identical with the one obtained from the patient. The identity of the strains was also established by the fact that each established a solid cross immunity in guinea pigs.

Because of the vesicular appearance of some of the lesions, the disease was called "rickettsialpox," and since the agent was isolated from mites, it was named *Rickettsia akari*, after the Greek name for mite. The recovery of apparently identical strains of rickettsia from the blood of a man ill with rickettsialpox and from blood-sucking mites collected from the home of the same man indicate that human infection was acquired from the mites, probably through biting.

The increase in the frequency with which Q fever has been observed in this country and the isolation of this new strain of rickettsia from a case of an entirely different type of disease in New York City both point to the increasing importance that rickettsias are assuming as causes of disease in the United States.

REFERENCES

- 1 Sussman L. N. Kew Gardens spotted fever. *New York Med J* 27 1946
- 2 Shankman B. Report of outbreak of endemic febrile illness not yet identified occurring in New York City. *New York State J Med* 46 2156-2159 1946
- 3 Greenberg M., Pelletier O. Klein I. S. and Heubner R. J. Rickettsialpox — newly recognized rickettsial disease. II Clinical findings. To be published.
- 4 Heubner R. J. Stamps P. and Armstrong C. Rickettsialpox — newly recognized rickettsial disease. I Isolation of etiological agent. *Pub Health Rep* 61 1605-1614 1946
- 5 Heubner R. J. Jellison W. L. and Pomerantz C. Rickettsialpox — newly recognized rickettsial disease. IV Isolation of rickettsia apparently identical with causative agent of rickettsialpox from *Allodermomyssus sanguineus* rodent mite. *Pub Health Rep* 61 1677-1682 1946

THE MEANING OF PSYCHOSOMATIC MEDICINE

CURRENT medical literature is marked by the number of articles on psychosomatic medicine. Although this is an indication of a healthy interest in the relation between psychic and somatic factors, which pervade sickness of all kinds, some of these articles suggest that there is occurring a subtle revision of the original meaning of the term "psychosomatic," which, if it becomes established, may do great harm. This is a matter of general interest and of basic significance.

When the term was first promulgated it was on the basis that disease of whatever kind always included in its manifestations elements of both somatic and psychic origin. Although the bodily aspect might have been in some cases the precipitating cause, it was thought that psychic disturbances always were included in the complete pattern of the disorder. In the same way, when psychic factors dominated the inception of an illness somatic disturbances always occurred and contributed their part to the manifestations of the disorder. Psychosomatic medicine therefore meant that disease is never wholly somatic or entirely psychic; it is always, with certain limitations, a combination of both. To emphasize the absence of a dichotomy between the somatic and psychic factors the term was put forth with the hope that it would no longer be necessary to say, with Kennedy,¹ that, "lacking appreciation of the neurological aspect of all disease, for it must color all by pervading all, we must perforce regard our patients not as persons but as congeries of viscera imperfectly combined and inadequately framed in design."

What is happening to the term "psychosomatic" seems to be a revision of definition that makes it mean something quite different from what it did

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

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MATERIAL should be received not later than noon on Thursday, two weeks before date of publication.

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A NEW RICKETTSIAL INFECTION IN NEW YORK CITY

DURING June and July, 1946, there appeared in New York City a peculiar febrile disease that aroused considerable interest and had both clinicians and laboratory workers temporarily baffled. The disease affected 92 residents of Kew Gardens in the Borough of Queens and 10 other persons elsewhere in New York City.¹⁻³

The illness was clinically characterized by an initial skin lesion on some part of the body. This appeared as a papule with surrounding erythema, was round or oval in shape and about 0.5 to 1.0 cm in diameter. Coincidentally the regional lymph nodes became enlarged and sometimes slightly tender. The patients, however, usually did not feel

sick, and they continued to work until five to ten days later, when there was an acute onset of chills, fever, sweating, headache and backache. The chills were often repeated several times a day, with temperature rises to between 102 and 104°F and remissions to 99 or 100°. The headache was usually quite severe. About three or four days after the onset of these symptoms a rash appeared over the body. The individual lesions were maculopapular and varied from 2 to 5 mm in diameter, some were flat, others somewhat pointed. Frequently, a deep-seated vesicle was seen in the center of the lesion, which often broke down and formed a crust. The fever, rash and other symptoms usually lasted from four days to a week. Although the patients felt sick, they did not usually appear particularly toxic at any time during the entire illness. The spleen was palpable in about half the cases but was never large.

Laboratory examinations were of no great help. The urine was usually normal. White-cell counts showed a leukopenia, with either a normal differential count or a lymphocytosis. Blood cultures were sterile. There was no increase in heterophil antibodies. The serums in both the acute and the convalescent stage showed no agglutination of typhoid and paratyphoid bacilli, the organisms causing brucellosis and tularemia, *Proteus X-19* or leptospira. Complement-fixation tests were negative for typhus fever, Rocky Mountain spotted fever, Q fever, scrub typhus and psittacosis.

Epidemiologically the cases were interesting because the majority of them were reported from one group of buildings in a section of Kew Gardens. Although the physicians who saw these cases had patients in other buildings in the immediate neighborhood and in areas nearby, they saw no other cases. Single cases, however, were observed by physicians of the New York City Department of Health in Manhattan and in the Bronx.

There were no fatalities, and no complications were observed in any of the cases. The disease did not respond to antibiotic or other specific therapy, and most of the cases were treated symptomatically.

The entire picture of the disease strongly suggested a rickettsial infection, and since all the tests for known diseases were negative, the aid of the National Institute of Health was enlisted. As a result, a

th and to improve medical care, these facts will be preceded by an official representative of the state medical association. The broadcasts should accomplish much in informing the public concerning the remarkable advances in medicine that have been made during the last hundred years and the facilities that are now available to raise the health standards of the Nation, and they are, of course, particularly appropriate for the centennial year of the American Medical Association. The first was given from 4:00 to 4:30 p.m. (EST) on Saturday, December 7, and one has been given or is scheduled on each following Saturday. The final broadcast, the twenty-sixth, will deal with the hundred years of the American Medical Association from a nationwide standpoint. To ensure a large audience, all physicians in each section are urged to publicize its program, the date of which will be published in the *Journal of the American Medical Association*.

JTE

The following appointments to the teaching staff of Harvard Medical School were recently announced: Max Boravk, of Newton Highlands (A.B. Harvard University 1930, D. Harvard University 1934, Ph.D. Columbia University 1938), assistant professor of bacteriology and immunology, etc. Lehner Bibring, of Cambridge (M.D. University of Vienna 1924), associate in psychiatry, Seymour Jerome Gray, Washington, D.C. (A.B. University of Rochester 1933, D. University of Pennsylvania 1936, Ph.D. University of Chicago 1945), assistant professor of medicine, Marian Abot Putnam, of Milton (A.B. Radcliffe College 1917, M.D. Johns Hopkins University 1921), lecturer on psychiatry, Edwitt Stetten, Jr., of New York City (A.B. Harvard University 1930, M.D. Columbia University 1934, Ph.D. Columbia University 1940), assistant professor of medicine.

CORRESPONDENCE

CONVALESCENT HOMES

To the Editor: The Committee on Public Health Relations of the New York Academy of Medicine is preparing a new edition of the *Directory of Convalescent Homes in the United States*, to be published by the Sturgis Fund of the Winifred Easterson Burke Relief Foundation of White Plains, New York. The last issue of this directory was published by the Sturgis Fund in 1931 under the auspices of the Committee on Convalescent Care of the American Conference on Hospital Service and has long been out of print. The need of a new directory is recognized by all concerned.

Early in January, a questionnaire will be distributed to all recognized convalescent homes maintained by municipalities, counties or voluntary bodies. The information sought deals with the physical plant, the staff, the requirements for admission, the type of patients, therapy and such other matters as will make the directory a dependable guide for physicians who wish to refer their patients to institutions for convalescence. The questionnaire is so devised that it can be filled out with a minimum of effort. Convalescent homes that do not receive a questionnaire are urged to request one by writing to E. H. L. Corwin, Executive Secretary, Committee on Public Health Relations, New York Academy of Medicine, 2 East 103 Street, New York 29, New York.

E. H. L. CORWIN, Executive Secretary
Committee on Public Health Relations

New York Academy of Medicine
2 East 103 Street
New York City

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Psychoanalytic Study of the Child Volume 1 (1945) 8°, cloth, 423 pp. New York: International Universities Press, 1945. \$6.00.

This is the first volume of a new series of studies on child analysis and child guidance. Various authors, in both America and Europe, report on many aspects of a pertinent problem. The book is designed for the specialist, and as a survey of the work now being carried on in psychoanalysis, as applied to children, can be fully recommended. Most of the papers are supplied with bibliographic references, and the work has been carefully edited.

Essentials of Neuro-Psychiatry. A textbook of nervous and mental disorders. By David M. Olson, M.D., associate professor of psychiatry, University of Illinois College of Medicine. 8°, cloth, 310 pp., with 138 illustrations. Philadelphia: Lea and Febiger, 1945. \$4.50.

The author presents an exposition on the principles involved in the psychiatric studies of mental disorders. The text is complete, with many illustrations and references to the literature. The volume is a sound contribution to the subject from a modern point of view. In spite of the fact that the book covers only three hundred pages, the material is surprisingly comprehensive and the author shows evidence of a thorough grasp of his subject.

Rorschach's Test. Volume II. A Variety of Personality Pictures. By Samuel J. Beck, Ph.D., head of Psychology Laboratory, Department of Neuropsychiatry, Michael Reese Hospital, Chicago, and associate professor of psychology, Northwestern University. With a foreword by Roy R. Grinker, M.D. 8°, cloth, 402 pp. New York: Grune and Stratton, 1945. \$5.00.

This is the second volume of a study on the Rorschach test. In the first, the author gave details regarding the method used in testing. He now presents an interpretation of his findings, giving many case histories to illustrate his points. There is a careful evaluation of clinical material with an analysis of the records. The book is well printed and there is an extensive bibliography. It should be of value to other workers in the same field.

New Directions in Psychology toward Individual Happiness and Social Progress. By Samuel Lowy, M.D. With an introduction by Herbert Read. 8°, cloth, 194 pp. New York: Emerson Books, Incorporated, 1945. \$3.00.

This volume is based on a series of lectures given by the author in Czechoslovakia between 1930 and 1936. He has had wide experience in European countries and more recently, in the last four years, in Great Britain, where he has been associated with the Czechoslovakian Center in Manchester. The author has analyzed a large number of patients from different countries, and his book reflects a careful evaluation of this material. Much of the text relates to the social aspects of psychiatry, and the author goes deeply into the philosophic principles of racial relations, tolerance, psychology and similar subjects associated with the problems of readjustment, particularly of displaced persons.

Manual of Diagnosis and Management of Peripheral Nerve Injuries. By Robert A. Groff, M.D., and Sara J. Houtz, B.S. With an introduction by I. S. Radwin, M.D., John Rhea Barton Professor of Surgery, University of Pennsylvania School of Medicine. 8°, cloth, 185 pp., with 111 illustrations. Philadelphia: J. B. Lippincott Company, 1945. \$8.00.

The subject is well covered by this brief monograph, the result of war experiences with patients having injuries to the peripheral nerves. The conclusions, in general, are sound. The simple line drawings, illustrating examination and various types of injury, are excellent. The format leaves a good deal to be desired. Although the subject is fully reviewed, it does not add much new material to knowledge of injuries of the peripheral nerves. Most physicians will not agree with the statement that electrotherapy, in facial paralysis, "can do more harm than good in maintaining muscle tone and assisting restoration of muscle action."

originally. Thus, Menninger² implies that what he means by psychosomatic medicine comprises the organ neuroses. It is not likely that he intended to give quite this impression, but his article serves as an illustration of a growing tendency to limit, if not to redefine, the term. Such a redefinition would restrict the term to those disorders that are thought to be psychic in origin and somatic in manifestation. This does not appear to conform to the original meaning; it is a revision, if not a distortion.

Not only does this alteration warp the conception so well presented by Dunbar³ in her book *Emotions and Bodily Changes*, but it threatens to undo the good work that she initiated. The former rigid classification of disease as either somatic or psychic is no longer tolerable in the light of present-day concepts. Dunbar's book pointed this out and set the course of medicine in the proper direction. It is regrettable that through misunderstanding or lack of clarity so many writers are upsetting the concept that all disease is both somatic and psychic. Restriction of the term "psychomatic" to the somatic manifestations of psychic disorders will, if it persists, materially delay general realization of the true nature of disease and will necessitate the classification of disease as somatic, psychic and psychosomatic. This would be regrettable.

Many examples of this process of revision could be given. With characteristic enthusiasm, clinicians seem to be forming a cult, glibly using the latest catchword without taking the trouble to understand its meaning. It might even be better if psychosomatic were abandoned and the simple word "sick" or some synonym were to be used. If it were understood that to be sick is to be assailed by influences derived from and expressing elements of both mind and body, the clinician might find it less convenient to fit the condition of the patient into any rigidly defined category. It would then be easy and natural to regard the patient as a person, as suggested by Robinson,⁴ and to look for all the elements that go to form the complex of his disease. It would also be easy and natural to realize that what often passes for mental disease is quite likely to result from organic causes and that organic expressions of disorder often result from psychic causes. Beyond all this it would be both easy and natural to realize

that all disease is compounded of both bodily and mental factors.

One of the great medical achievements of the past few years has been the recognition of the part played by the emotions in disorders that were previously regarded as solely organic. Perhaps an achievement of equal importance will come from the realization of the part played by organic factors in what now is considered to be solely mental disease. If it is too late to undo the harm caused by the subtle revision of the term "psychosomatic" then it may be necessary to devise an alternative. Thus, if psychosomatic is to be confined to organic disorders arising from psychic causes, then it may be counteracted by some such term as "somatopsychic" to be used in connection with mental diseases of somatic origin. It is hoped that no such clumsy circumlocution will be needed. No occasion for it will exist if the original meaning of psychosomatic is not distorted. After all, this word obviously was introduced in this form for the sake of euphony and not because of any design ascribing to one factor priority over the other.

REFERENCES

- 1 Kennedy, F. Neurological approach in general medicine. *New York Med J* 17-19, 1945.
- 2 Menninger, W. C. Psychosomatic medicine on general medical wards. *Bull U. S. Army M. Dept* 4:545-550, 1945.
- 3 Dunbar, H. F. *Emotions and Bodily Changes: A survey of literature on psychosomatic interrelationships, 1910-1933*. 595 pp. New York: Columbia University Press, 1935.
- 4 Robinson, G. C. *The Patient as a Person: A study of the social aspect of illness*. 423 pp. New York: The Commonwealth Fund, 1939.

MASSACHUSETTS MEDICAL SOCIETY

DEATH

KANE — WILLIAM V. Kane, M.D., of Lynn, died October 11. He was in his fifty-fifth year.
Dr. Kane received his degree from Tufts College Medical School in 1915. He was a member of the New England Pediatric Society.

MISCELLANY

"DOCTORS — THEN AND NOW"

The 1946-1947 program of broadcasts sponsored by the American Medical Association and the National Broadcasting Company will trace the highlights in medical progress in the United States since pioneer days. The whole country has been divided into twenty-five sections, and in each a dramatization of some local event that contributed to the advance of medical knowledge will be given. Thus, in the section composed of Massachusetts, Rhode Island and Connecticut the story will concern Oliver Wendell Holmes' contribution to the conquest of puerperal fever and his coining of the word "anesthesia," whereas in Maine, New Hampshire and Vermont the story will be based on Nathan Smith's efforts that led to the formation of highly successful medical schools at Dartmouth College, Yale University, Bowdoin College and the University of Vermont. At the close of each dramatization the program will conclude with up-to-the-minute news of what is now being done in each particular section to further medical knowledge, to promote public

The New England Journal of Medicine

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Volume 236

JANUARY 16, 1947

Number 3

EPIDEMIC DIARRHEA OF THE NEWBORN IN MASSACHUSETTS

A Ten-Year Survey

A DANIEL RUBENSTEIN, M D,* AND GEORGE E. FOLEY†

BOSTON

EPIDEMIC diarrhea of the newborn continues to be a major problem in infant care. Although the clinical manifestations of the syndrome have been adequately described, outbreaks frequently remain unrecognized until widespread dissemination has taken place, and the occurrence of fatalities has stimulated the adoption of belated control measures. Unfortunately, when epidemics are insidious in onset, the diagnosis may not be easy. For this reason those responsible for the care of newborn infants must be constantly on the alert to differentiate the syndrome from the large variety of other conditions producing diarrhea in infants.

The etiology of epidemic diarrhea of the newborn has not been determined. A striking characteristic of many of the outbreaks previously reported in the literature is the diversity of agents suspected as the cause, various authors having reported the isolation of the following micro-organisms: *Shigella dispar*,¹ *Sh. paradyserteriae*,² *Klebsiella pneumoniae*,³ gamma streptococci,³ *Escherichia coli mutabile*,⁴ monilia,^{5, 6} *Esch. coli*,⁷ *Pseudomonas aeruginosa*,⁷ alpha streptococci,⁷ *Aerobacter aerogenes*,⁸ *Proteus vulgaris*,⁹ and filterable agents.¹⁰⁻¹² The lack of a common etiology in the reported epidemics suggests that epidemic diarrhea is caused either by a single agent as yet unknown or by a variety of organisms whose toxic products result in gastrointestinal irritation. The former thesis is favored by the isolation of filterable agents in recent outbreaks,¹⁰⁻¹² and the latter by the similarity of histologic changes observed in fatal cases associated with a variety of micro-organisms.¹³

It is the purpose of this discussion to review nineteen outbreaks of epidemic diarrhea of the newborn as reported to the Massachusetts Department of Public Health from 1935 to 1945. In the 258 cases reported during the period of the study 85 patients died, giving a case mortality of 33 per cent (Table 1).

In addition to the clinical and epidemiologic investigations, bacteriologic studies were undertaken to evaluate the adequacy of nursing technics and formula-making procedures and to study possible modes of transmission from infant to infant. Direct observations of nursery technics were checked by a few simple examinations such as bacterial counts on formulas and cultures of thermometers, nipples and other utensils. Cases and contacts, including nursery personnel, were studied bacteriologically, type determination being utilized as an epidemiologic tool whenever possible.

In several outbreaks nose and throat cultures were obtained from patients and contacts. Stool cultures were studied for the presence of streptococci and to exclude the possibility of infection with enteric micro-organisms.

Since there is no practical method for the serologic classification of *Staphylococcus aureus*, the strains encountered in the outbreaks reported were studied biochemically. The ability of a group of strains to utilize various polysaccharides was taken as an indication of common identity. Whenever possible the serologic grouping of streptococci¹⁴ and the determination of types within the various groups,¹⁵ especially those contained in Lancefield Group D,^{16, 17} were employed to establish the common identity of the strains concerned in a single outbreak.

During the course of these investigations, a method was evolved for scoring the efficiency of technics of individual nurseries in handling newborn infants. The details of this method are outlined below, together with an appraisal of procedures encountered in the hospitals where outbreaks occurred.

CLINICAL STUDIES

The syndrome known as epidemic diarrhea of the newborn primarily affects infants up to three weeks of age. It was frequently observed that infants developed symptoms following discharge from an infected nursery and were admitted to open wards

*District health officer, Massachusetts Department of Public Health and instructor in epidemiology, Harvard School of Public Health.

†Formerly technical associate in epidemiology, Department of Preventive Medicine, Harvard Medical School and Department of Epidemiology, Harvard School of Public Health.

NOTICES

ANNOUNCEMENTS

Dr Archie A Abrams calls attention to the omission of his office address and telephone number from the current telephone directory. His office is at 1093 Beacon Street, Brookline, and the telephone number is ASPinwall 9951

Dr Stephen D Peabody, who has returned from military service, announces the opening of his office for the general practice of medicine at 7 Cross Street, Wellesley

SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, January 21, at twelve noon. Dr Franz J Ingelfinger will speak on the topic "Developments in the Treatment of Peptic Ulcer and Its Complications."

Physicians are cordially invited to attend

NEW ENGLAND PEDIATRIC SOCIETY

A meeting of the New England Pediatric Society will be held on Wednesday, January 22, in Boston

PROGRAM

- 1 15 p m Luncheon at Vanderbilt Hall, Harvard Medical School (price, 70 cents)
- 3 30 p m Clinical presentation of patients Amphitheater, Joseph H Pratt Diagnostic Hospital. Members of the medical profession and students are invited to attend
- 5 30 p m Refreshments at Longwood Towers
- 6 30 p m Dinner at Longwood Towers (price, \$2 00, including tax). Members and their guests are invited to attend
- 7 30 p m Annual meeting Longwood Towers
- 7 45 p m The Management of Respiratory Diseases in Infants and Children Longwood Towers. Dr James L Wilson, professor, Department of Pediatrics and Communicable Diseases, University Hospital, University of Michigan. Members of the medical profession and students are invited to attend

ELLA SACHS PLOTZ FOUNDATION FOR THE ADVANCEMENT OF SCIENTIFIC INVESTIGATION

During the twenty-third year of the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation, forty applications were received by the Trustees, twenty-nine of which came from the United States, the other eleven coming from different countries in Europe, Asia and North and South America. Twenty grants were distributed.

Applications for grants to be held during the year 1947-1948 must be in the hands of the Executive Committee before April 15, 1947. There are no formal application blanks, but letters asking for aid must state definitely the qualifications of the investigator, an accurate description of the research, the size of the grant requested and the specific use of the money to be expended. In their requests for aid applicants should state whether or not they have approached other foundations for financial assistance and what other sources of support are relied on for research. It is highly desirable to include letters of recommendation from the directors of the department in which the work is to be done. Only applicants complying with the above conditions will be considered. Applications should be sent to Dr Joseph C Aub, Massachusetts General Hospital, Fruit Street, Boston 14.

SCIENTISTS NEEDED FOR USPHS

Competitive examinations will be held early in 1947 for appointment to the Regular Corps of the United States Public Health Service, according to a recent announcement by Dr Thomas Parran, Surgeon General. Seventy-five vacancies exist in grades of assistant and senior assistant scientist.

Written examinations, covering each candidate's particular field of science, as well as related fields, will be held April 14

and 15 at places mutually convenient to the applicant and the Service. Oral examinations will be held during the February 13-April 9 in thirty cities, strategically throughout the United States. (The oral examination of candidates from New England will be held in Boston at the Marine Hospital, 77 Warren Street, Brighton, on April 1.)

Commissions are available to scientists trained in any of the following fields: bacteriology, mycology, parasitology, entomology, malacology, biology, chemistry, physiology, physics, statistics (mathematical, demographic and so forth), psychology and milk and food examination. Assignments will be in line with demonstrated ability and experience.

An applicant for the grade of assistant scientist must be a citizen of the United States, have had seven years of educational and professional training or experience, possess a certificate or diploma from an institution of recognized standing and be able to pass a physical examination given by a medical officer of the United States Public Health Service. The same requirements, plus an additional four years of training or experience, apply to those seeking the grade of senior assistant scientist.

Commissioned officers in the Regular Corps enjoy the same benefits and privileges as do officers of the Army, Navy or Marine Corps. The grade of assistant scientist is equal to that of first lieutenant in the Army. Annual pay, with allowances for dependents is \$3811. A senior assistant scientist ranks with a captain of the Army and draws, with allowances for dependents \$4351 a year.

United States Public Health Service officers are entitled to full medical care and hospitalization for themselves and their families, including disability retirement at three-fourths basic pay. They receive thirty days' annual leave with pay. Periodic promotions are based on length of service and merit. The retirement age is sixty-four.

Application forms and additional information may be obtained by writing to the Surgeon General, United States Public Health Service, Washington 25, D C.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JANUARY 16

FRIDAY, JANUARY 17

- *9 00-10 00 a m Changes in Biologicals and in Human Recipients. Dr Ralph F Wheeler. Joseph H Pratt Diagnostic Hospital.
- *10 00 a m-12 00 m Medical Staff Rounds. Peter Bent Brigham Hospital.

MONDAY, JANUARY 20

- *12 15-1 15 p m Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, JANUARY 21

- *12 00 m South End Medical Club. Headquarters Boston Tuberculosis Association.
- 12 00 m-1 00 p m Dermatological Service, Grand Rounds. Amphitheater Dowling Building, Boston City Hospital.
- *12 15-1 15 p m Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

WEDNESDAY, JANUARY 22

- *9 00-10 00 a m Pediatric Clinicopathological Conference. Dr James M Baty and H E MacMahon. Joseph H Pratt Diagnostic Hospital.
- *11 00 a m-12 00 m Medical Clinic. Amphitheater Children's Hospital.
- *12 00 m Clinicopathological Conference (Children's Hospital). Amphitheater Peter Bent Brigham Hospital.
- *2 00-3 00 p m Combined Clinic by the Medical Surgical and Orthopedic Services. Amphitheater, Children's Hospital.
- *7 15 p m Graduate Seminar in Pediatrics. Children's Medical Service. Amphitheater 3A Massachusetts General Hospital.

*Open to the medical profession

OCTOBER 11-MAY 14 Metropolitan State Hospital. Page 398 issue September 12.

JANUARY 14 8 00 p m Harvard Medical Society. Amphitheater Peter Bent Brigham Hospital.

JANUARY 21 South End Medical Club. Notice above.

JANUARY 22 New England Pediatric Society. Notice above.

FEBRUARY 7 American Board of Obstetrics and Gynecology. Page issue of January 7.

FEBRUARY 9 National Conference on Medical Service. Page 956, issue of December 26.

FEBRUARY 13 The Clinical Importance of the Blood Type in Transfusions and in Obstetric Patients. Dr Louis K Diamond. Pediatric Association of Physicians. 8 30 p m Haverhill.

(Notices continued on page xvii)

ortality from 0 to 88 per cent. In one epidemic (Table 1, Outbreak 5) 7 out of 8 infants with diarrhea of the newborn died.

Table 2 presents the morbidity and case mortality for full-term and premature infants. Of the 88

babies acquired the disease. In the outbreaks studied the proportion of the former was so small that no definite conclusions could be drawn concerning this point. Actually, no hard and fast lines could be drawn, since breast-fed babies were frequently

TABLE 2 Morbidity and Case Mortality among Premature and Full-Term Infants with Epidemic Diarrhea of the Newborn

OUTBREAK No	No. of Infants Exposed		No. of Cases		Morbidity		No. of Deaths		Case Mortality	
	Premature	Full Term	Premature	Full Term	Premature %	Full Term %	Premature	Full Term	Premature %	Full Term %
1	—	—	—	—	—	—	—	—	—	—
2	9	106	3	9	—	8	1	—	67	11
3	9	216	4	24	44	11	9	—	75	38
4*	—	—	—	—	—	—	1	—	100	27
5	1	18	1	7	100	49	1	6	100	86
6	0	22	0	6	0	27	0	—	0	50
7	0	20	0	6	0	30	0	0	0	0
8	1	16	1	3	100	19	1	2	100	67
9	1	11	1	2	100	18	0	0	0	0
10	1	18	1	4	100	22	0	2	0	50
11	16	15	3	11	19	73	2	0	67	0
12	19	15	6	11	32	73	3	2	50	18
13	14	26	11	8	79	31	2	0	18	0
14	0	10	0	6	0	60	0	—	0	50
15	7	14	6	6	86	43	4	0	67	0
16	1	52	1	6	100	12	1	0	100	0
17	7	65	4	28	57	43	2	6	50	21
18	1	15	0	4	0	27	0	0	0	0
19	1	41	1	5	100	12	1	0	100	0
Totals	88	680	43	146	49	21	23	77	53	25
Averages										

*In this outbreak 1 premature and 11 full term infants became ill; the number of infants exposed was not known.

premature infants who were exposed 43, or 49 per cent, developed the infection. The rate among full-term infants was significantly lower: of the 680 infants exposed only 157, or 21 per cent, developed the infection. The case mortality among premature infants was 53 per cent, or more than twice that for full-term infants, which was 25 per cent. It is

artificially fed for several days during the first week of life.

Investigation of nursing technics and of methods of formula making brought to light many startling deficiencies. At times nursing procedures were found to be in direct violation of existing state regulations. In some hospitals so-called "aseptic technics," when

TABLE 3 Nursing Facilities and Supervision in Ten Outbreaks of Epidemic Diarrhea of the Newborn

HOSPITAL No	ADEQUATE SPACE IN NURSERY*	ADEQUATE STAFF IN NURSERY†	INDIVIDUAL RECTAL THERMOMETER*	INDIVIDUAL OIL BOTTLE*	ADEQUATE SUPERVISION OF FORMULA†	POST-PASTEURIZATION OR POST-STERILIZATION OF FORMULA*	ADEQUATE STERILIZATION OF NIPPLES*	SEPARATE FORMULA ROOM AND DIET KITCHEN*	TOTAL SCORE
1	0	0	0	10	20	0	0	10	40
2	10	20	10	10	20	0	0	0	70
3	10	20	10	10	0	0	0	0	50
4	0	0	0	10	0	0	10	0	20
5	0	0	0	10	0	0	0	0	10
6	0	0	0	10	0	0	0	0	10
7	10	20	10	0	20	0	10	10	80
8	0	0	0	0	0	0	10	0	10
9	0	0	0	10	20	0	10	0	40
10	0	0	0	0	0	0	0	0	0

*Numerical value of 10

†Numerical value of 20

apparent that the former are particularly susceptible to epidemic diarrhea of the newborn, and that once the infection has been acquired death is likely to occur.

In two outbreaks it was noted that infants in adjacent bassinets developed the infection. By and large, however, such relations could not be established. Usually, both breast-fed and artificially fed

subjected to bacteriologic investigation, yielded results that were surprising to nursery supervisors and hospital administrators.

The findings concerning nursery and formula-making technics in ten hospitals in which outbreaks of epidemic diarrhea of the newborn occurred are presented in Table 3. A numerical value was assigned for each of the eight factors ordinarily

of another hospital before a clinical diagnosis had been made. No secondary cases occurred among older infants or hospital personnel known to have been exposed to these babies. Similarly, secondary cases were not discovered among family contacts.

Occasionally, infants beyond the neonatal age developed symptoms indistinguishable from epidemic diarrhea of the newborn. In one outbreak (Table 1, Outbreak 5) a seven-week-old infant became ill and died following exposure to patients

Some fatal cases occurred at the onset of an outbreak. Other early cases were not so serious, and mild infections continued to appear for several weeks before the occurrence of a fatal case. Secondary or recurrent outbreaks have been reported in a single institution after intervals of several months during which no new cases appeared.¹⁸

Once the existence of an epidemic has been established, the differential diagnosis is not difficult. Salmonella infection of the newborn, which may

TABLE 1 *Morbidity and Mortality in Epidemic Diarrhea of the Newborn in Massachusetts*

OUTBREAK No	YEAR	NO OF INFANTS EXPOSED	NO OF CASES	MORBIDITY %	NO OF DEATHS	CASE MORTALITY %
1	1935	?	57	?	25	44
2	1937	115	12	10	3	25
3	1938	225	28	12	12	43
4	1940	?	12	?	4	33
5	1940	19	8	42	7	88
6	1940	22	6	27	3	50
7	1940	20	6	30	0	0
8	1941	17	4	24	3	75
9	1941	12	3	25	0	0
10	1941	19	2	26	2	40
11	1941	31	14	45	2	14
12	1942	34	17	50	5	29
13	1942	40	19	48	2	11
14	1943	10	6	60	3	50
15	1943	21	12	57	4	33
16	1944	53	7	13	1	14
17	1945	72	32	44	8	25
18	1945	16	4	25	0	0
19	1945	42	6	14	1	17
Totals		768	258		95	
Averages				24.6		33

with epidemic diarrhea of the newborn. The clinical picture was identical with that shown by younger infants.

The onset of the infection may be insidious or abrupt. In some outbreaks early cases may be difficult to detect. Infants may become indifferent to food and fail to gain weight. They appear listless, and vomiting is occasionally noted. When the onset is sudden, profuse diarrhea and vomiting may be the first signs, followed by a dramatic loss in weight.

Characteristically, the stools are frequent, watery and yellow in color, changing later to green. Blood and pus are not usually present. As the diarrhea persists, the infant becomes dehydrated and loss of weight of a pound a day may occur.

Marked elevation of temperature is not a prominent feature. At times, even in fatal cases, the temperature remains normal or only slightly elevated until just prior to death, when there is a rise associated with a terminal bronchopneumonia.

Severe cases are unmistakable. The infant rapidly becomes worse, vomiting is severe and diarrhea profuse. Dehydration is serious, and the fontanels are sunken. Death may occur in twenty-four hours or may be deferred for several days. The total duration of illness in 25 fatal cases varied from two to twenty-nine days, with an average of eight days.

also occur in outbreaks, must be differentiated from epidemic diarrhea of the newborn. In the former disease the onset is abrupt, with a marked elevation of temperature. Although the initial manifestations may be gastrointestinal, the subsequent clinical course is sometimes characterized by bacteremia and sepsis, with signs and symptoms of meningitis, pneumonia or otitis media. At least two Salmonella outbreaks among the newborn have been reported in which meningitis was the principal clinical manifestation.^{19, 20} Cultures of the blood and stools readily establish the diagnosis in such epidemics.

It must be pointed out that clinically and epidemiologically the outbreak described by Buddingh and Dodd¹⁰ presents certain features that differentiate it from the syndrome under consideration. Secondary cases developed among hospital personnel, and thrushlike lesions, which are not ordinarily encountered in patients with epidemic diarrhea of the newborn, were described. Buddingh's virus was demonstrated by scarifying the cornea of a rabbit.

EPIDEMIOLOGY

Previous reports have called attention to the high morbidity and mortality associated with epidemic diarrhea of the newborn.^{18, 21} Similar high rates were experienced in Massachusetts (Table 1). Morbidity rates varied from 10 to 60 per cent, and case

esulted in contamination of the formulas. In other hospitals student nurses, after twenty-four hours of instruction, took complete charge for one or two months, and were then replaced by other students. In only four hospitals was a single person — a

respiratory tracts or the stools of the personnel (Table 6)

According to standard practice, formulas should not be prepared in a room that also serves as a diet kitchen for adjacent hospital wards. This requirement was satisfied in only two of the ten hospitals. In the majority a single refrigerator was used both for the storage of food for patients and for the infants' formulas.

Procedures for the sterilization of nipples varied considerably. In three hospitals nipples were boiled once in twenty-four hours and thereafter kept in a so-called "sterile container" to be used as needed. In other nurseries, nipples were boiled immediately after each feeding, following which they were stored in sterile containers for two or three hours until a subsequent feeding.

Examination of nipples sterilized and stored in this manner frequently revealed the presence of large numbers of bacteria, on both the inner and the outer surfaces. In Nursery A, for example (Table 6), cultures of supposedly sterile nipples and of a sterile funnel used in filling nursery bottles revealed the presence of pure cultures of *Staph aureus*. These strains were biochemically identical with those isolated from the throats of 2 infants and from the hand dip in use in this nursery.

Ordinarily, nipples are handled with sterile forceps kept in a jar of disinfectant. This practice is bac-

registered nurse or a dietitian — charged with the responsibility of formula preparation and of the instruction of student nurses.

Samples of formulas were submitted from several of the nurseries studied. Instead of being almost bacteria free, as should have been expected, they gave bacterial counts that would scarcely have

TABLE 5 Bacterial Counts of Formulas			
NURSERY	BACTERIAL COUNT per cc	ORGANISM ISOLATED	OTHER SOURCES OF ORGANISMS
A	32 000	Alpha strep cocci Lancefield Group D streptococci (Type 1) <i>E. coli</i> <i>Staph aureus</i> <i>Pr vulgaris</i>	Throats (9 infants), stools (3 infants), thermometer dip, hand dip and thermometer
B	396 000	<i>Staph aureus</i> <i>E. coli</i> <i>B subtilis</i>	Throats (9 infants) and hand dip
C	9 500	<i>Staph aureus</i> <i>E. coli</i> <i>P. m.</i>	

TABLE 6 Micro-organisms Isolated from Cases, Contacts, Nurses and Materials					
NURSERY	NO OF INFANTS CULTURED	MICRO-ORGANISM	SOURCE OF CULTURE		
			PATIENTS	CONTACTS	NURSES OTHER
A	11	Alpha streptococci	Throat (9 cases)		
		Lancefield Group D streptococci (Type 1)	Stool (3 cases)		Formulas, hand dip, thermometer dip and thermometers
		<i>Staph aureus</i>	Throat (2 cases)		Formulas, nipples and hand dip
		<i>E. coli</i>	Throat (7 cases)		Formulas, hand dip, thermometer dip and thermometers
B	17	Alpha streptococci	Throat (5 cases)	Throat (4 infants)	
		Lancefield Group D streptococci (Type 1)			
		<i>Staph aureus</i>	Throat (4 cases)	Throat (1 infant)	Formulas and hand dip
		<i>E. coli</i>	Throat (7 cases)		Formulas, hand dip and thermometer dip
C	5	Lancefield Group A streptococci (Type 6)	Throat (1 case)		Throat (3 nurses)
		<i>Staph aureus</i>	Throat (1 case)		Throat (1 nurse)
		<i>E. coli</i>	Throat (4 cases)		
					Throat (1 nurse)
D	18	Alpha streptococci	Throat (12 cases)		
		Lancefield Group D streptococci (Type 1)	Stool (5 cases)		
E	22	Alpha streptococci	Throat (15 cases)	Throat (3 infants)	
		Lancefield Group D streptococci (Type 1)	Stool (9 cases)		
F	13	Beta streptococci	Throat (13 cases)		
		Lancefield Group D streptococci (Type 1)	Stool (2 cases)		
			Urine (1 case)		

satisfied the minimum market requirements for raw milk (Table 5). A large variety of organisms were recovered from these formulas. In several cases the bacteria were of the same species as those isolated from infants in the nursery, as well as from the

terologically unsound not only because it places too much dependence on the efficiency of chemical disinfectants but also because the manipulation necessary to replace the nipple on the bottle involves considerable risk of contamination from the fingers.

regarded as significant in infant care. A score of 10 was granted for each of six items. Adequacy of nursing staff and of supervision of formula making was considered of extreme importance and was assigned a value of 20. It will be noted that no hospital received a score higher than 80. Perhaps it was only a coincidence that there were no fatal cases in any of the outbreaks occurring in hospitals with a score of 50 or higher.

Although the use of a common rectal thermometer is contrary to existing regulations, in seven of the nurseries individual thermometers were not available

individual cup generally recommended for this purpose.

It is customary in many nurseries for nurses to dip their hands in a so-called "sterilizing" solution (usually alcohol) after handling each infant and before picking up another. Cultures of several of these sterilizing solutions revealed exceedingly high bacterial counts (Table 4). Like the thermometer solutions, the hand dips were often used for several days without being changed. It was frequent practice in some nurseries to filter the used alcohol hand solution. This recovered alcohol was sub-

TABLE 4 Bacterial Counts on Thermometer and Hand Disinfectants

NURSERY	THERMOMETER DIP		TYPE OF ORGANISM*	HAND DIP		TYPE OF ORGANISM
	DISINFECTANT	BACTERIAL COUNT per cc		DISINFECTANT	BACTERIAL COUNT per cc	
A	Bichloride of mercury (1:2000)	44,000	<i>Esch coli</i> <i>Staph albu</i> † <i>Pr vulgaris</i> Alpha streptococci Lancefield Group D streptococci (Type 1)‡	Bichloride of mercury (1:10,000)	75,000	<i>Staph aureus</i> § <i>Esch coli</i> Alpha streptococci Lancefield Group D streptococci (Type 1)‡
B	Bichloride of mercury (1:2000)	7,000,000	<i>Esch coli</i> <i>B subtilis</i>	Lithal alcohol (95 per cent)	150,000	<i>Esch coli</i> <i>B subtilis</i> <i>Staph aureus</i>

*In order of predominance.

†Same organisms isolated from a single thermometer.

‡Same organism isolated from formulas, thermometers and stools of infants.

§Same strain present in pure culture on sterile nipples.

||Same strain isolated from infants' and nurses' throats and sterile formulas.

for each infant. In several of these hospitals, immersion of the thermometer in a bichloride or alcohol solution, frequently before removal of the lubricating material, was the method employed in sterilization.

The thermometer dips used in two of the nurseries studied were subjected to bacteriologic examination (Table 4). Both nurseries used a 1:10,000 dilution of bichloride of mercury for this purpose. The lubricant was wiped off with a pledget of cotton, and the thermometers were then soaked overnight in a common basin of bichloride solution. This was renewed once in seven or ten days. Bacterial counts on samples of one of these thermometer dips revealed a bacterial population of 7,000,000 viable micro-organisms per cubic centimeter, the majority of which were *Esch coli*.

Similar studies on samples of the thermometer solution taken from a second nursery revealed a count of 44,000 viable micro-organisms per cubic centimeter, of which the majority were *Esch coli*, *Pr vulgaris* and *Staph albus*. It is obvious that thermometers treated in this manner could readily transmit infection from infant to infant.

Standard nursing technics attempt to limit contact between infants wherever possible. The use of common utensils and materials should be avoided. In several nurseries, a common oil bottle served as a ready means of maintaining contact between infants. The oil bottle was used instead of the

sequently added to a fresh supply for the following day's use.

Adequate space was available in only three out of the ten nurseries. The Children's Bureau²² has recommended 30 square feet per bassinet in hospital nurseries. Several of the nurseries were obviously overcrowded. In three, there was scarcely enough room for a nurse to pass between the rows of bassinets.

What constitutes an adequate nursing staff in an infant nursery? The Children's Bureau²² recommends that a nurse should not be responsible for the care of more than 8 infants. It is apparent that most hospitals have not adopted so high a standard. For the purpose of this study, an arbitrary standard of 1 nurse for 12 babies was considered satisfactory, provided that this ratio was maintained both day and night.

The nursing staffs were considered adequate according to this standard in only three out of the ten hospitals studied. One institution, with a daytime ratio of 1:12, employed but 1 nurse to care for 24 infants during the night. The daytime ratios varied from 1:5 to 1:20, whereas at night the range was from 1:12.5 to 1:26.

In six of the ten hospitals, formula preparation was not adequately supervised. In two, untrained ward attendants were responsible for this important procedure. Observation of these persons at work revealed faulty practices that could easily have

resulted in contamination of the formulas. In other hospitals student nurses, after twenty-four hours of instruction, took complete charge for one or two months, and were then replaced by other students. In only four hospitals was a single person—a

TABLE 5 *Bacterial Counts of Formulas*

NURSERY	BACTERIAL COUNT per cc	ORGANISMS ISOLATED	OTHER SOURCES OF ORGANISMS
A	32,000	Alpha streptococci Lancefield Group D streptococci (Type 1) <i>Esch coli</i> <i>Staph aureus</i> <i>Pr vulgaris</i>	Throats (9 infants) stools (3 infants), thermometer dip, hand dip and thermometers
B	396,000	<i>Staph aureus</i> <i>Esch coli</i> <i>B subtilis</i>	Throats (9 infants) and hand dip
C	9,500	<i>Staph aureus</i> <i>Esch coli</i> <i>P. aeruginosa</i>	

registered nurse or a dietitian—charged with the responsibility of formula preparation and of the instruction of student nurses.

Samples of formulas were submitted from several of the nurseries studied. Instead of being almost bacteria free, as should have been expected, they gave bacterial counts that would scarcely have

respiratory tracts or the stools of the personnel (Table 6).

According to standard practice, formulas should not be prepared in a room that also serves as a diet kitchen for adjacent hospital wards. This requirement was satisfied in only two of the ten hospitals. In the majority a single refrigerator was used both for the storage of food for patients and for the infants' formulas.

Procedures for the sterilization of nipples varied considerably. In three hospitals nipples were boiled once in twenty-four hours and thereafter kept in a so-called "sterile container" to be used as needed. In other nurseries, nipples were boiled immediately after each feeding, following which they were stored in sterile containers for two or three hours until a subsequent feeding.

Examination of nipples sterilized and stored in this manner frequently revealed the presence of large numbers of bacteria, on both the inner and the outer surfaces. In Nursery A, for example (Table 6), cultures of supposedly sterile nipples and of a sterile funnel used in filling nursery bottles revealed the presence of pure cultures of *Staph aureus*. These strains were biochemically identical with those isolated from the throats of 2 infants and from the hand dip in use in this nursery.

Ordinarily, nipples are handled with sterile forceps kept in a jar of disinfectant. This practice is bac-

TABLE 6 *Micro-organisms Isolated from Cases, Contacts, Nurses and Materials*

NURSERY	NO OF INFANTS CULTURED	MICRO-ORGANISM	SOURCE OF CULTURE			
			PATIENTS	CONTACTS	NURSES	OTHER
A	11	Alpha streptococci	Throat (9 cases)			
		Lancefield Group D streptococci (Type 1)	Stool (3 cases)			Formulas, hand dip, thermometer dip and thermometers
		<i>Staph aureus</i>	Throat (2 cases)			Formulas, nipples and hand dip
		<i>Esch coli</i>	Throat (7 cases)			Formulas, hand dip, thermometer dip and thermometers
B	17	Alpha streptococci	Throat (5 cases)	Throat (4 infants)		
		Lancefield Group D streptococci (Type 1)	Throat (4 cases)	Throat (5 infants)		
		<i>Staph aureus</i>	Throat (7 cases)			Formulas and hand dip
		<i>Esch coli</i>				Formulas, hand dip and thermometer dip
C	5	Lancefield Group A streptococci (Type 6)	Throat (1 case)		Throat (1 nurse)	
		<i>Staph aureus</i>	Throat (1 case)		Throat (1 nurse)	
		<i>Esch coli</i>	Throat (4 cases)			
D	18	Alpha streptococci	Throat (12 cases)		Throat (1 nurse)	
		Lancefield Group D streptococci (Type 1)	Stool (5 cases)			
E	22	Alpha streptococci	Throat (15 cases)	Throat (5 infants)		
		Lancefield Group D streptococci (Type 1)	Stool (9 cases)			
F	13	Beta streptococci	Throat (13 cases)			
		Lancefield Group D streptococci (Type 1)	Stool (2 cases)			
			Urine (1 case)			

satisfied the minimum market requirements for raw milk (Table 5). A large variety of organisms were recovered from these formulas. In several cases the bacteria were of the same species as those isolated from infants in the nursery, as well as from the

terrologically unsound not only because it places too much dependence on the efficiency of chemical disinfectants but also because the manipulation necessary to replace the nipple on the bottle involves considerable risk of contamination from the fingers.

of the nurse. In only four nurseries were nipples adequately sterilized prior to each feeding.

Pasteurization or autoclaving of formulas after the bottles have been filled is an excellent safeguard in the feeding of the newborn in hospitals. Bottles are capped with sterilized nipples, and aluminum or glass caps are placed over the rubber nipples, from which they are separated by a pledget of cotton. The aluminum or glass-capped bottles are then placed in an autoclave and sterilized at 7 pounds of pressure for twenty minutes. This precaution eliminates the possibility of any contamination that may have taken place during the preparation of the formulas.

DISCUSSION

Since both the etiology and the manner of spread of epidemic diarrhea of the newborn are unknown, adequate supervision of nursery-room technics and methods used in formula preparation constitutes a safeguard against the occurrence of outbreaks. The studies described above revealed the need for greater diligence on the part of nursery supervisors. Careful attention to nursery technics should be part of the routine of every hospital. Too often it is only after the occurrence of an outbreak that authorities become aware of such matters.

Superintendents of hospitals frequently do not seek assistance from health agencies in controlling outbreaks until after considerable time has elapsed. Only six outbreaks (Table 7) were reported within

of the first case and that of the last fatal case were noted in several outbreaks. It is apparent that epidemics are frequently of long duration, and it is conceivable that many cases might have been prevented by the early adoption of drastic control measures.

Several of these outbreaks occurred during the war, when hospital superintendents were experiencing considerable difficulty in maintaining adequate staffs. Whenever decreases in personnel became necessary, there was a tendency to limit the staff in the nursery before reductions were made elsewhere. Frequently, hospital administrators substituted relatively untrained personnel, such as ward attendants and Red Cross aids, for trained persons in the nursery only to regret this practice after serious outbreaks had occurred.

Inadequacies in nursery procedures and formula preparation may be ascertained by technical methods. The hospital bacteriologist can readily determine whether the formulas, nipples, thermometers and other utensils used in the care of newborn infants have been properly sterilized.

It is a frequent misconception that disinfectants by cursory contact kill the bacterial flora on instruments and hands. Actually, many of the ordinary disinfectants kill only after fairly prolonged contact. Furthermore, the killing — or more accurately, the inactivating — effect of certain disinfectants may be reversed even after prolonged contact by the addition of certain substances to the substrate.

Dubos²³ recently pointed out that staphylococci failed to grow after being exposed for a few hours to a bichloride of mercury solution. If, however, the poisoned culture is treated with hydrogen sulfide, the cells recover their viability even though they have been exposed for seventy-two hours to a 1 per cent bichloride of mercury solution. Dubos²³ further points out that the presence of certain materials, such as phosphatides and phospholipids, which are frequently present in biologic materials, may actually protect bacterial cells from the action of the disinfectant.

Moreover, the activity of a disinfectant can be considered, in general, to vary with the concentration, the number of bacteria exposed and the nature of the substrate. It stands to reason that the prolonged use of a given volume of disinfectant results in the accumulation of extraneous materials, such as oils and grease from instruments, desquamated cells from the skin and dead bacteria, that not only reduce the effective concentration of the active disinfectant but also may inactivate it to the extent that bacterial growth occurs. Disinfecting solutions must be fresh and used intelligently if they are to be effective.

It has been shown that so-called "sterilizing solutions" (hand dips) are frequently heavily contaminated. Moreover, 95 per cent ethyl alcohol (with Congo red), used in one nursery as a hand dip, is

TABLE 7 Intervals before Reports of Outbreaks

OUTBREAK No.	INTERVAL BETWEEN FIRST CASE AND FIRST REPORT days	INTERVAL BETWEEN FIRST CASE AND FIRST FATAL CASE days	INTERVAL BETWEEN FIRST CASE AND LAST FATAL CASE days
1	32	—	37
2	51	*	44
3	44	*	43
4	54	*	35
5	42	*	22
6	36	13	†
7	3	†	23
8	28	*	†
9	3	20	21
10	23	*	13
11	9	*	9
12	3	*	7
13	1	*	11
14	33	*	30
15	32	—	16
16	39	*	†
17	6	†	29
18	4	†	
19	57		

*First case fatal

†No fatal cases

seven days of the occurrence of the first case, whereas in 10 cases at least a month elapsed before such notification. In one outbreak there was a span of twenty-nine days between the onset of the first fatal case and the beginning of the outbreak. In two other outbreaks, thirteen and twenty days, respectively, elapsed before the onset of an ultimately fatal case. Long intervals between the onset

practically useless as a disinfectant. It has been known for some time that the alcohols in concentrations of over 50 per cent exhibit little or no disinfecting activity. To cite an extreme case, Koch,²² in 1881, found that spores remained viable for as long as four months when immersed in absolute ethyl alcohol.

The ineffectiveness of these disinfecting solutions was further emphasized by the demonstration that, with the addition of small amounts of protein in the form of nutrient broth, they actually supported bacterial growth (Table 8). Samples of disinfectants

TABLE 8 Cultivation of Micro-organisms in Disinfecting Solutions

NURSERY	DISINFECTANT*	PROTEIN ADDED† mg/cc	BACTERIAL GROWTH
A	Thermometer dip — 1 2000 solution of bichloride of mercury	10	—
	Hand dip — 1 10 000 solution of bichloride of mercury	10-70 80	— +
B	Thermometer dip — 1 2000 solution of bichloride of mercury	10-100 200	— +
	Hand dip — 95 per cent ethyl alcohol	10-70 80	— +

*Constant volume of 1 cc

†Added in form of 1 per cent peptone broth

in current use in various nurseries were collected and filtered through a Seitz filter to remove the accumulated debris and bacteria. Increasing amounts of peptone broth were then added to a fixed volume of disinfectant. Each tube was inoculated with a small particle of stool collected from an infant in the nursery. The amount of stool varied but was always considerably less than that remaining on a rectal thermometer after use. Some solutions, to which as little as 10 mg. of protein had been added, readily supported bacterial growth.

In the outbreaks reported here, *Staph aureus* and various streptococci were encountered frequently from both patients and contacts (Table 8). No etiologic relation is claimed for these micro-organisms, but they may be considered as indicating transmission of an infectious agent from infant to infant or from formula to infant. In several outbreaks the same type of streptococci was isolated from infants and nose and throat cultures of nurses. Nevertheless, no definite conclusions could be drawn concerning either transmission or portal of entry.

In three hospitals, although certain techniques in the nursery were considered inadequate, cultures taken of formulas and equipment did not reveal bacterial contamination. In one of these hospitals infection spread from a nursery to another nursery on the floor above without the interchange of infants, utensils or personnel from one ward to another,

air-borne transmission, or at least indirect transmission other than case-to-case contact, was suggested.

On the other hand, the frequency with which Lancefield Group D streptococci were encountered in the throats of infants with epidemic diarrhea of the newborn suggests infection by the fecal-oral route. Salmonella infection of the newborn is further evidence that where poor techniques are employed, infants may be exposed to organisms often associated with the human intestinal tract.

On several occasions outbreaks started among premature babies and spread subsequently to full-term infants. The increased susceptibility of premature infants is reflected in their higher morbidity and case mortality. Particular attention must be given to premature infants in setting up safeguards against epidemic diarrhea of the newborn.

By utilizing the scoring method evolved in this study, hospitals may evaluate their own nursery procedures and formula preparation. Since there is no definite information concerning the etiology and mode of transmission, it is extremely important that institutions providing care for the newborn should avail themselves of every possible means of preventing epidemic diarrhea of the newborn. It is obvious that closer attention to the details of nursery techniques will lessen considerably the risk of cross infections in hospital nurseries and will serve as a precaution against this extremely serious disease.

SUMMARY

During the interval 1935 to 1945, a total of nineteen outbreaks of epidemic diarrhea of the newborn were reported to the Massachusetts Department of Public Health. Of 768 newborn infants who were exposed during the course of these outbreaks, 258 (33.6 per cent) developed symptoms and 85 died, the case mortality being 33 per cent.

The morbidity rates among premature and full-term infants were 49 and 21 per cent respectively. The case mortality for premature infants was 53 per cent, more than twice that for full-term babies, which was 25 per cent.

Investigation of nursing techniques and methods of formula preparation in nurseries where these outbreaks occurred revealed many inadequacies. Overcrowding, insufficient personnel, general use of a common rectal thermometer and inadequate supervision of formula making were frequently encountered.

Laboratory examinations of so-called "sterilizing solutions," including alcohol hand solution and thermometer dips, formulas, nipples and other utensils showed heavy bacterial contamination.

The ineffectiveness of such disinfecting solutions was further illustrated by experiments demonstrating that with the addition of small amounts of protein they actually supported bacterial growth.

A method is presented by means of which the efficiency of technics used in handling newborn infants may be evaluated

In several outbreaks apparently identical organisms were isolated from sick and healthy infants, nursery personnel and formulas *Staphylococcus aureus*, Lancefield Group D streptococci and Lancefield Group A (Griffith, Type 6) were among the bacterial agents isolated

The presence of Group D streptococci in the throats of infants with epidemic diarrhea of the newborn suggests that, as the result of poor nursery technics, infants may be exposed to organisms that are normally found in the human intestinal tract

Because the etiology and the mode of transmission of epidemic diarrhea of the newborn are not known, supervision of nursery-room technics and of formula preparation constitutes a factor in the hospital care of newborn infants that merits greater attention from hospital administrators

REFERENCES

- 1 Johnston, M. M. and Kaake, M. J. Bacteriologic study of three small epidemics of infectious diarrhea in children two caused by *B. dysenteriae* (Sonne) and one by *B. dyspar* *J. Pediat* 7:65-69 1935
- 2 Aitoff, M. and Dauna, R. Bacille dysentérique agent pathogène probable d'une entérite grave, à caractère épidémique dans un service de nouveau-nés *Compt. rend. Soc. de biol.* 121:110-112, 1936
- 3 Jampolis, M., Howell, K. M., Calvin, J. K., and Leventhal, M. L. *Bacillus mucosus* infection of new born *Am. J. Dis. Child* 43:70-88, 1932
- 4 Baker, C. J. Epidemic diarrhea of newborn report of three outbreaks *J. Pediat* 14:183-189 1939
- 5 Durand, J. I. Epidemic of diarrhea in hospital nursery apparently caused by monilium *J. Pediat* 7:726 1935
- 6 Murphy, J. R., and Mallozzi, M. A. Fungus findings in diarrhea outbreak in new-borns *Arch. Pediat* 53:276 1936
- 7 Craig, W. S. Acute alimentary catarrh in new born *Lancet* 1:687, 1936
- 8 Cass, J. M. *Bacillus lactis aerogenes* infection in newborn *Lancet* 1:346, 1941
- 9 Costello, J. P., and Lind, H. E. Epidemic of nursery diarrhea *Smith M. J.* 32:620-622, 1939
- 10 Buddingh, G. J., and Dodd, K. Stomatitis and diarrhea of infants caused by hitherto unrecognized virus *J. Pediat* 25:103-113, 1944
- 11 Lembecke, P. A., Quinlivan, J. J., and Orchard, N. G. Epidemic diarrhea of newborn report of two outbreaks *Am. J. Pub. Health* 33:1263-1273 1943
- 12 Light, J. S., and Hodes, H. L. Studies on epidemic diarrhea of newborn isolation of filterable agent causing diarrhea in calves *Am. J. Pub. Health* 33:1451-1454 1943
- 13 Farber, S. Personal communication
- 14 Lancefield, R. C. Serological differentiation of human and other groups of hemolytic streptococci *J. Exper. Med.* 57:571-595, 1931
- 15 Idem. Specific relationship of cell composition to biological activity of hemolytic streptococci. In *The Harvey Lectures* Vol. 36. Baltimore: Williams and Wilkins Company, 1940-1941. Pp. 251-280.
- 16 Foley, G. E., and Wheeler, S. M. Studies on Streptococci ("enterococci") of Lancefield group D. I. Serologic and biochemical characteristics *Am. J. Dis. Child* 70:93-99, 1945
- 17 Wheeler, S. M., and Foley, G. E. Studies on Streptococci ("enterococci") of Lancefield group D. II. Recovery of Lancefield group D streptococci from antemortem and postmortem cultures from infants and young children *Am. J. Dis. Child* 70:207-215, 1945
- 18 Rice, J. L., Best, W. H., Frant, S., and Abramson, H. Epidemic diarrhea of newborn. I. Preliminary considerations on outbreak of highly fatal diarrhea of undetermined etiology among newborn babies in hospital nurseries *J. A. M. A.* 109:475-481 1937
- 19 Abramson, H., Frant, S., and Oldenbusch, C. Salmonella infection of newborn: its differentiation from epidemic diarrhea and other primary enteric disorders of newborn *M. Clin. North America* 23:591-606, 1939
- 20 Aballi, A. A., Falcon, S., Panesello, R. S., Curbelo, A., and Cruz, J. A. M. Salmonellosis del recién nacido *Bol. Soc. Cubana de pediat* 9:123-160 1937
- 21 Frant, S., and Abramson, H. Epidemic diarrhea of newborn epidemiology of outbreaks of highly fatal diarrhea among newborn babies in hospital nurseries *Am. J. Pub. Health* 28:36-43, 1938
- 22 *Standards and Recommendations for Hospital Care of Newborn Infants Full time and premature* United States Department of Labor Children's Bureau Publication No. 292 14 pp 1943
- 23 Dubos, R. J. Antimicrobial agents of biologic origin *J. A. M. A.* 124:633-636 1944
- 24 Koch, R. Cited by Zinsser, H., and Payne Jones, A. *A Textbook of Bacteriology With a section on pathogenic protozoa* Seventh edition 1226 pp New York: D. Appleton and Company, 1934. P. 77

LEIOMYOMA OF THE JEJUNUM*

Report of a Case

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MASSIVE hemorrhage into the gastrointestinal tract is usually associated with a penetrating ulcer of the posterior wall of the duodenum. Serious massive hemorrhage, however, occasionally occurs with the less frequent benign leiomyoma and malignant leiomyosarcoma of the stomach and small intestine. In the case of leiomyoma of the jejunum with massive enterorrhagia and melena reported below, the preoperative diagnosis was bleeding duodenal ulcer.

Leiomyoma of the small intestine is rare. Smith,¹ in 1937, in a review of the literature, was able to collect 513 cases of leiomyomas of the gastrointestinal tract. Of these 50 occurred in the esophagus, 321 in the stomach, 109 in the small intestine and 33 in the colon. In reviewing the records of 36,000 cases at autopsy at the Philadelphia General Hospital, he found 33 cases of gastrointestinal leiomyoma, 8 of which arose in the small bowel. In 1942 Weber and Kirklin² analyzed the material at the Mayo Clinic over a thirty-two-year period and gathered a total of 108 malignant tumors and 41 benign neoplasms of the small intestine. In the latter group, myomas occurred in 14 cases, 8 of these being found in the duodenum, 4 in the jejunum and 2 in the ileum.

Small-bowel leiomyomas are found about equally in both sexes, most frequently between the ages of thirty and forty, but they may occur at any age. One case has been reported in a two-year-old child.³

Small-bowel leiomyomas may be classified according to their location in the bowel wall as primarily of submucosal (inner or intraluminal) or subserosal (outer or extraluminal) origin. The former are small, pedunculated or sessile tumors, usually less than 5 cm. in diameter, that extend into the lumen of the bowel. They are three times as frequent in the jejunum and ileum as in the duodenum.¹ Subserosal leiomyomas are slowly growing, egg-shaped tumors, varying in size from 7 to 30 cm. in diameter. They are usually located on the antimesenteric border of the bowel and extend into the peritoneal cavity. They occur almost twice as frequently as the submucosal type and are often found unexpectedly at laparotomy or autopsy.¹

Malignant change is surprisingly frequent in leiomyomas of the small intestine, being reported in 15 to 20 per cent of cases.⁴ Subserosal leiomyomas

are particularly prone to become malignant, metastases or recurrences having taken place in 16 per cent of the reported cases.¹ No metastases or recurrences have been reported in tumors of the submucosal variety.

Not all leiomyomas of the small bowel give rise to symptoms. In Raiford's⁵ series 46 per cent were incidental findings at necropsy. The submucosal variety, however, is rarely asymptomatic, regardless of size. The clinical manifestations, which are variable and depend on the location, size and character of the tumor, are predominantly those of intestinal obstruction and enterorrhagia. Submucosal leiomyomas of the duodenum often cause partial obstruction and ulcerlike pain, when they are located below the ligament of Treitz, intussusception is the usual result. Repeated attacks of intestinal obstruction secondary to intussusception are the most frequent clinical findings, occurring in 62 per cent of the collected cases.¹ Superficial ulceration of the tumor results in enterorrhagia and melena, repeated attacks being not unusual. Subserosal leiomyomas may reach such size as to attract the patient's attention and may, by mechanical stress, produce partial intestinal obstruction, but as a rule they tend to be asymptomatic. Occasionally, progressive central necrosis in the tumor occurs, with evacuation into the intestinal tract, producing a pseudodiverticulum from which severe enterorrhagia is likely to continue until death unless operation is performed. The principal clinical manifestations are gastrointestinal hemorrhage and melena, which occur in 31 per cent of cases.

Less frequent clinical findings in leiomyoma of the small intestine are peritoneal irritation, secondary to necrosis of the tumor or volvulus, and frank peritonitis due to rupture.

Usually the diagnosis of jejunoileal leiomyoma is made at operation or autopsy. As in the case reported below and in others, the preoperative diagnosis is usually bleeding duodenal ulcer or intestinal obstruction, the etiology being undetermined. Ordinary barium study of the gastrointestinal tract may reveal a defect caused by a duodenal myoma, but below the ligament of Treitz it is rarely useful in the diagnosis of these tumors. The most accurate method of detecting a jejunoileal lesion is by serial roentgenograms taken every hour for five hours following a barium meal.⁶ If obstruction resulting from a tumor of the small bowel is present, a roentgenogram of the abdomen will reveal the usual evidence of dynamic ileus.

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CASE REPORT

A 53-year-old widowed schoolteacher was first seen in the Lahey Clinic on October 15, 1943, complaining of epigastric distress, tarry stools and fainting of 4 weeks' duration. She had been in good health until 1941, when for about 6 months, she had gaseous indigestion and epigastric distress. This discomfort occurred daily about 2 or 3 hours after meals, and was partially relieved by food or soda. There was no vomiting, hematemesis or melena. Appendectomy had been done in July of that year, with relief of symptoms except for an occasional mild attack of gaseous indigestion. The patient had remained quite well until 1 month before admission, when at 2 o'clock in the morning, she was awakened by a "dull pressing ache" in the epigastrium, which seemed to push upward against the diaphragm and chest. There was nausea but no vomiting. The discomfort was relieved somewhat by bicarbonate of soda and she was able to sleep the remainder of the night. She awoke at the usual time, had breakfast and went about her work. In about 2 hours she was seized with a similar attack of epigastric discomfort, became weak and was nauseated but did not vomit. An almost constant desire to defecate was present. After a soft, tarry stool, she fainted and was unconscious for about 2 minutes. She was taken home and put to bed but continued to have repeated, loose, tarry stools. After about 10 days of bed rest and treatment by a physician, the bleeding subsided. Following roentgenologic studies of the gastrointestinal tract on September 27, the presence of a "filling defect of the duodenopyloric region not typical of ulcer" was reported. The physician referred the patient to this clinic for further study.

Physical examination was negative except for moderate tenderness to the left of the midline in the upper abdomen. The blood pressure was 132/76, and the pulse 76. Rectal examination was negative. Examination of the blood showed a red-cell count of 4,100,000, with a hemoglobin of 9.9 gm., and a white-cell count of 5400, with normal differential and platelet counts. Gastric analysis revealed 10 units of free acid and 40 units of total acid. Barium studies of the gastrointestinal tract were negative. Although a lesion of the gastrointestinal tract could not be demonstrated by roentgenologic examination, a clinical diagnosis of duodenal ulcer with recent hemorrhage was made. An ambulatory regimen for ulcer, consisting of a strict diet and antacids, was instituted. The patient was seen at the clinic at regular intervals and, except for mild and transient episodes of epigastric distress, did well for more than 18 months. On April 2, 1945, following the eating of apple pie, she again had a severe attack of epigastric distress, followed by melena.

Physical examination on April 12 was negative. The blood pressure was 150/83, and the pulse 70. Examination of the blood showed a red-cell count of 4,200,000, with a hemoglobin of 11.8 gm. The sedimentation rate was normal. Gastric analysis showed 20 units of free acid and 61 units of total acid. Barium studies of the gastrointestinal tract revealed a persisting indentation at the peak of the duodenal cap, which was present both on fluoroscopy and in the films. The patient was again placed on a strict ulcer regimen. She was co-operative, followed instructions well and did satisfactorily until March 23, 1946, when melena again occurred. Hemorrhage was profuse, with repeated tarry stools, necessitating hospitalization.

On March 30 the patient was admitted to the hospital on the gastrointestinal service. Examination disclosed an apprehensive patient whose skin and mucous membranes were somewhat pale. The blood pressure was 118/62, and the pulse 112. Abdominal examination revealed no abnormalities. Examination of the blood disclosed a red-cell count of 1,950,000, with a hemoglobin of 5.6 gm., and a white-cell count of 8500. The hematocrit reading was 18 per cent. During the four days following admission melena continued and, despite medical treatment, including repeated daily transfusions of whole blood and plasma, could not be controlled. The red-cell count could not be elevated above 2,500,000 or the hemoglobin above 7 gm. A diagnosis of bleeding duodenal ulcer was made by members of the gastroenterology service, who believed that operation would be necessary to control the hemorrhage. The surgical consultant agreed, and operation was arranged.

Celiotomy was performed on April 5 under fractocoll pontocaine spinal anesthesia, with supplemental cyclopropane anesthesia. The stomach and duodenum were found to be entirely normal. The first, second and third portions of the duodenum were carefully visualized and palpated, but no abnormalities could be found. There was no evidence of an old or recent ulcer. The liver was normal, and there was no indication of dilated veins or varices about the cardiac end of the stomach or the esophagus. In the jejunum, approximately 15 cm from the ligament of Treitz, a polypoid tumor was palpated, it was quite firm, measured approximately 3 cm in diameter and appeared to involve both the serosa and the mucosa. There were a few slightly enlarged lymph nodes in the mesentery adjacent to the tumor. Distal to the tumor but not proximal to it, the small and large bowels were filled with blood. It was decided that the tumor was responsible for the hemorrhage, and a segmental resection of the jejunum with open end-to-end anastomosis was done.

Pathological examination was performed on a specimen consisting of small intestine measuring 90 x 70 x 0.8 cm. The serosal surface was smooth and shiny, with a central rounded protrusion rising 0.3 cm above the surface. In the center of the mucosal surface there was a previously opened, rounded, papilliform projection measuring 2 cm in length, 1.5 cm transversely and 2.5 cm in longitudinal diameter. It was covered by mucosa and had a firm, rubbery base, measuring 1.5 cm in diameter. The cut surface showed a granular mottled, grayish pink and red surface. The microscopic diagnosis was leiomyoma of the jejunum.

This case, as in the usual tumor of the small bowel, was incorrectly diagnosed as duodenal ulcer. Fortunately, celiotomy was performed, the source of the hemorrhage was found and the patient completely recovered. Fatal cases of suspected bleeding duodenal ulcer have been reported in which operation was withheld and autopsy disclosed a bleeding benign neoplasm of the small bowel.^{1, 2, 3, 7} When there is continued melena and inability to control shock and hemorrhage through conservative measures of rest, morphine and restoration of blood volume by repeated transfusions, surgical interference is imperative if death is to be avoided.

Roentgenologically, the small intestine is said to be the blind spot of the abdomen. The key to the diagnosis of small-bowel lesions is suspicion. A patient who has persistent atypical ulcer pain, recurrent episodes of melena or repeated attacks of small-bowel obstruction without a demonstrable lesion of the gastrointestinal tract should be suspected of having a small-bowel neoplasm. If such a lesion is suspected by the clinician and the roentgenologist so advised, special studies often reveal the tumor.

* * *

The incidence, pathologic characteristics and clinical manifestations of leiomyoma of the small intestine are reviewed.

A case of leiomyoma of the jejunum is reported in which the preoperative diagnosis was incorrect but the treatment was successful.

This case emphasizes the fact that the presence of small intestinal neoplasms is much too infrequently suspected.

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REFERENCES

- Smith O. V. Leiomyoma of small intestine with report of case with fatal hemorrhage. *Am J M Sc* 194 700-707 1937
- Weber, H. M. and Kirklin B. R. Roentgenologic manifestations of tumors of small intestine. *Am J Roentgerol* 47 243-253 1942
- Kroger F. Cited by Hanno and Mensch⁷
- Klopp E. J., and Crawford, B. L. Leiomyoma of small intestine. *Ann Surg* 101 726-733 1935
- Railford T. S. Tumors of small intestine. *Arch Surg* 25 122-177 and 321-355 1932
- Kiefer E. D., and Lahey, F. H. Tumors of small intestine. *New Eng J Med* 208 1042-1048 1933
- Hanno H. A. and Mensch M. Leiomyoma of jejunum intermittent melena of fourteen years duration and fatal hemorrhage. *Ann Surg* 120 199-206 1944

ARTHROPLASTY OF THE ELBOW*

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FOR nearly forty years ankylosed elbows have been reconstructed by arthroplastic procedures consisting of reshaping the articular ends and interposing a flap of fascia for a gliding surface. In 1908, I performed one of the first arthroplasties of the elbow using free fascia as the interposing membrane. With increased experience in the use of the method, which led to improvement in the operative technic and better judgment in the selection of cases, the results of arthroplasty of the elbow have come to be almost routinely satisfactory.

The reconstruction of a joint by arthroplasty is not a simple procedure. A new joint must be created that not only has a functional range of motion but is also stable and well controlled. For the elbow to be useful, the motion must range from at least 45° of flexion to 170° of extension. Stability is a factor that is quite as important in the mobilization of the non-weight-bearing elbow joint as in the reconstruction of hip and knee joints. It is of no advantage to a patient to obtain a movable joint if at the same time it is abnormally mobile, unbalanced and not under control.

Not every ankylosed elbow is suitable for arthroplasty. The origin of the stiffness must first be considered. Cases of purely traumatic origin lend themselves best to arthroplasty. Good results may be obtained in cases of ankylosis of pyogenic infectious origin, provided that the disease is not progressive and provided that it is quiescent. Arthroplasty cannot be carried out with safety until at least a year has elapsed from the time of the disappearance of all signs of the disease. Among cases of infectious origin, those of gonorrheal invasion offer the best chance of a successful outcome. Mobilizing measures in cases of tuberculous involvement can be carried out only in exceptional cases, on the whole, arthroplasty is considered to be contraindicated in such cases.

The ages at which arthroplasty is performed most successfully are between nineteen and forty-five years. The procedure may be considered when the patient is fifty years of age, provided the bone and musculature are in good condition. Operative inter-

vention at an earlier age than nineteen may cause damage that will interfere with growth.

Bone, musculature and skin must be in good condition. It is difficult to remodel the articular ends in the presence of eburnated bone or extreme bone atrophy. The muscles controlling the joint should be free from scar tissue and in good tone, so that the aftercare will be in no way retarded. When the skin or subcutaneous tissue is adherent to bone, the operation is difficult. If it is not possible to restore the bone, musculature and skin to good condition, the ultimate success of arthroplasty is questionable, and the operation is, as a rule, contraindicated.

Finally, the general health and mental outlook of the patient must be considered. An important pre-operative step is the careful checking of all possible foci of infection. The more co-operative the patient is in withstanding the convalescence and in carrying out the postoperative treatment to establish motion, the greater are the chances of success.

Operative Technic

The elbow joint is approached by a semicircular incision that curves over the olecranon and extends from one condyle to the other (Fig 1). The skin and subcutaneous tissues are dissected, and the flap is retracted. The ulnar nerve is retracted to the ulnar side. A transverse incision is made through the deep fascia, ligaments and capsule down to the periosteum. The olecranon is chiseled through transversely at the joint line.

The joint is then ready to be broken open. This step is more easily carried out when the joint line is still visible and the joint surfaces can be separated by means of curved chisels (Fig 1). When the joint cavity is entirely obliterated in a bony bridge, the site of the old joint line is determined as closely as possible and then chiseled or sawed through. The forearm is flexed, the olecranon segment freed, and the flap dissected back in toto. This flap is preserved for a subsequent covering of the joint.

In the remodeling of the articular surfaces, the normal contours of the joint are followed as closely as possible. The articular ends should fit together accurately. Care should be taken to remove only enough bone to permit free motion. An electric burr

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is used to remodel the condyles of the humerus (Fig 2) The olecranon fossa is deepened, care being taken to preserve the olecranon ridge, which is an

freed of all fat, it is wrapped around the newly formed humeral condyles and attached anteriorly and posteriorly to the capsule (Fig 3) Number two

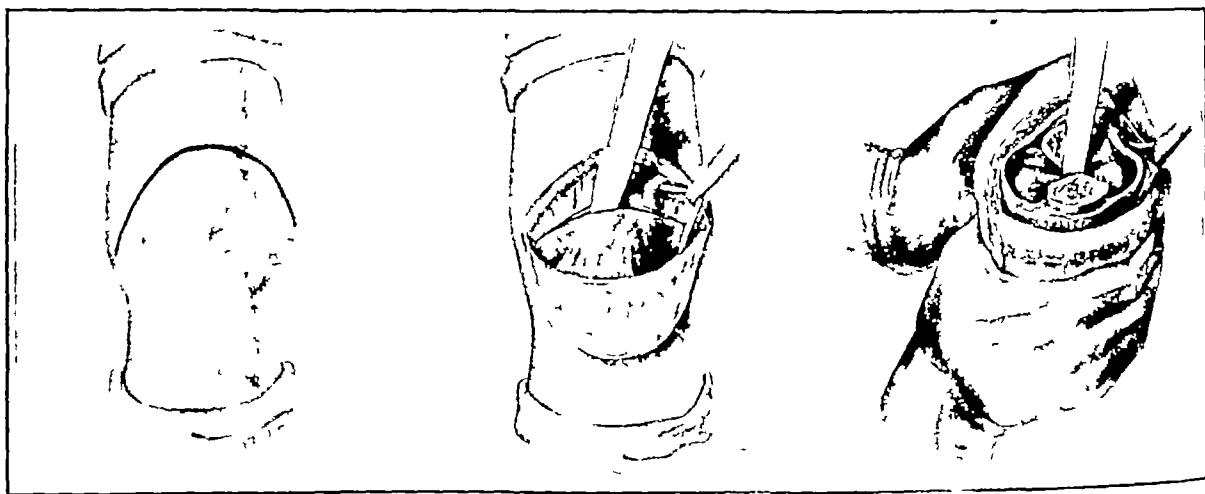


FIGURE 1 *Technic of Operation*

These sketches show the line of incision, the splitting of the olecranon at the joint line with a chisel and the breaking open of the joint, with freeing of the olecranon segment

aid in maintaining the lateral stability of the joint. It may be necessary to deepen the radial and ulnar surfaces somewhat with an electric burr, so that they will conform to the humeral surfaces. The ulnar

chromic catgut is wound tightly around the base of the fascial flap and firmly tied.

The articular ends are brought into apposition. A screw is driven through the olecranon and into the

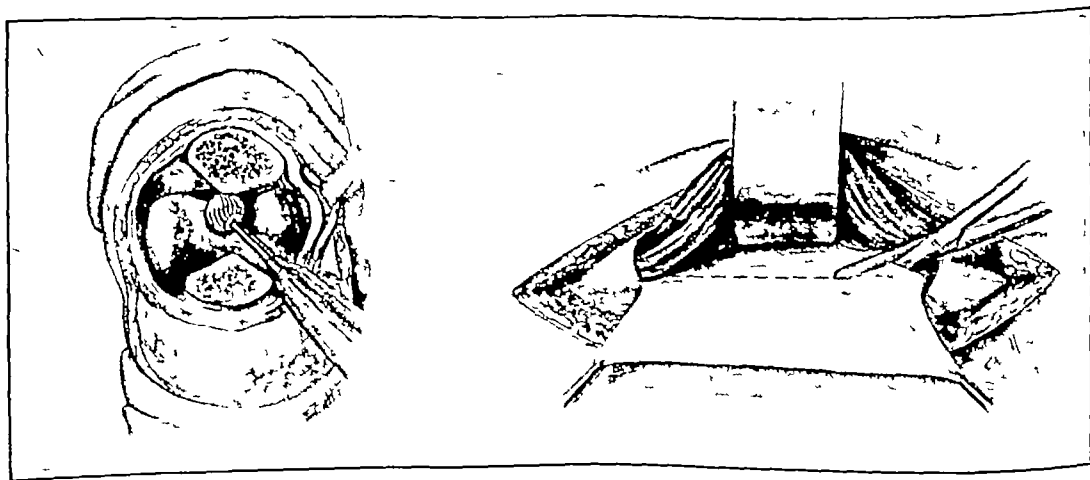


FIGURE 2 *Technic of Operation*

These sketches show the remodeling of the humeral condyles with an electric burr and the cutting of the fascia lata from the thigh

ridge, which articulates with the intercondylar notch, should not be disturbed.

A flap of fascia lata is removed from the outer part of the thigh (Fig 2). After the flap has been

ulna (Fig 3). The capsule is closed with interrupted sutures of catgut, and the skin is closed with interrupted sutures of silk. A small compression dressing is applied. The arm is immobilized in a neck and

wrist sling, with the forearm flexed just above the right angle

The postoperative treatment is an essential part of the arthroplastic procedure, and the success of the operation depends to a great extent on the cooperation of the patient in this aftercare. The pa-

many of these cases are to be found in the literature¹⁻⁴. Our results have proved that the elbow lends itself well to arthroplastic measures. The results have been excellent, the patients obtaining both a satisfactory range of motion and a joint that is stable and well controlled. No arthritic changes have de-

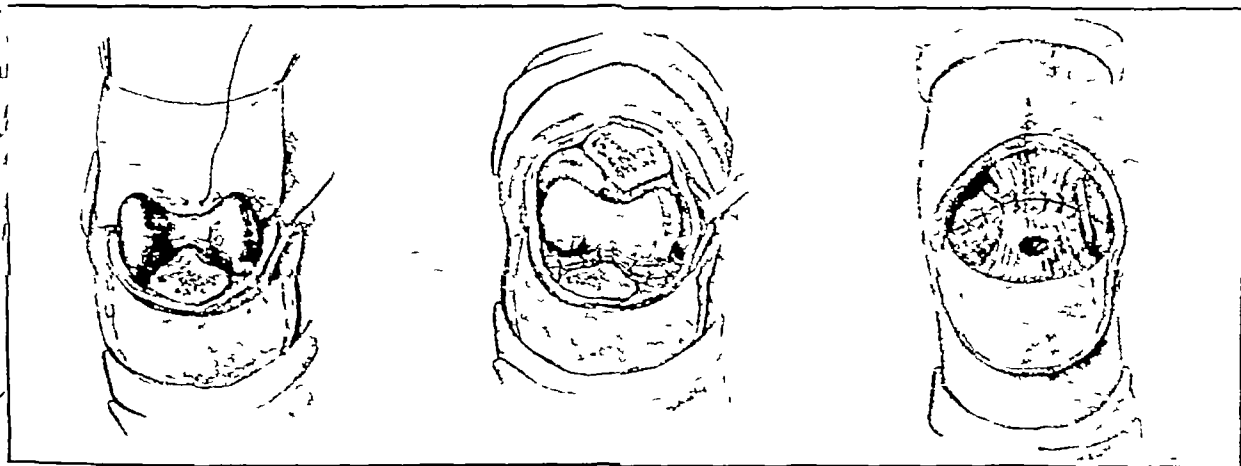


FIGURE 3. *Technic of Operation*

These sketches show the sewing of the flap of fascia lata to the capsule anteriorly, the fascial flap in place over the humeral condyles and the screw through the olecranon

atient should practice contraction exercises of the arm and forearm muscles hourly, to maintain their tone and to improve the circulation. The dressing is changed in a week. Passive motions are carried out in about ten days after the operation. Gentle massage may be given in three weeks. The patient also begins to use the arm after the third week, returning it to the sling only for rest.

* * *

More than 100 ankylosed elbows have been mobilized by arthroplasty in our clinic. Reports of

veloped in later years, even in the joints of men working in heavy industries.

412 Beacon Street

REFERENCES

- 1 MacAusland W. R. Ankylosis of elbow with report of four cases treated by arthroplasty. *J A M A* 64 312-318 1915
- 2 *Idem*. Ankylosis of elbow and its treatment by arthroplasty. *M Rec* 100 609 1921
- 3 *Idem*. Mobilization of elbow by free fascia transplantation with report of thirty-one cases. *Surg Gynec & Obst* 33 223 245 1921
- 4 MacAusland W. R., and MacAusland A. R. *The Mobilization of Ankylosed Joints by Arthroplasty*. 252 pp. Philadelphia: Lea and Febiger 1929

THE EFFECT OF AMPHETAMINE SULFATE ON SPASMODIC FLEXION MOVEMENTS OF THE FOOT*

Report of a Case

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DISTURBANCES in tone and motion of voluntary muscles,—including rigidity, hyper-tonicity, dystonia, rhythmic or oscillating tremor, athetosis, choreiform movements and spasmodic or torsion movements,—present either singly or in combination, usually indicate dysfunction of the extrapyramidal pathway. These symptoms are sometimes so bizarre that they may be mistaken for manifestations of hysteria. The peculiar disorder presented by a striking case recently observed falls

ganglions. In the most frequent disease of the extrapyramidal pathway, Parkinson's syndrome, amphetamine (Benzedrine) sulfate, if given in sufficient dosage (20 mg or more), often diminishes the rigidity but has little if any influence on the tremor.¹ In some cases of spasmodic torticollis the drug is beneficial.² In my experience little or no benefit results from the use of amphetamine sulfate in dystonia athetosis, dystonia musculorum deformans or familial tremor of the head. It is my practice to

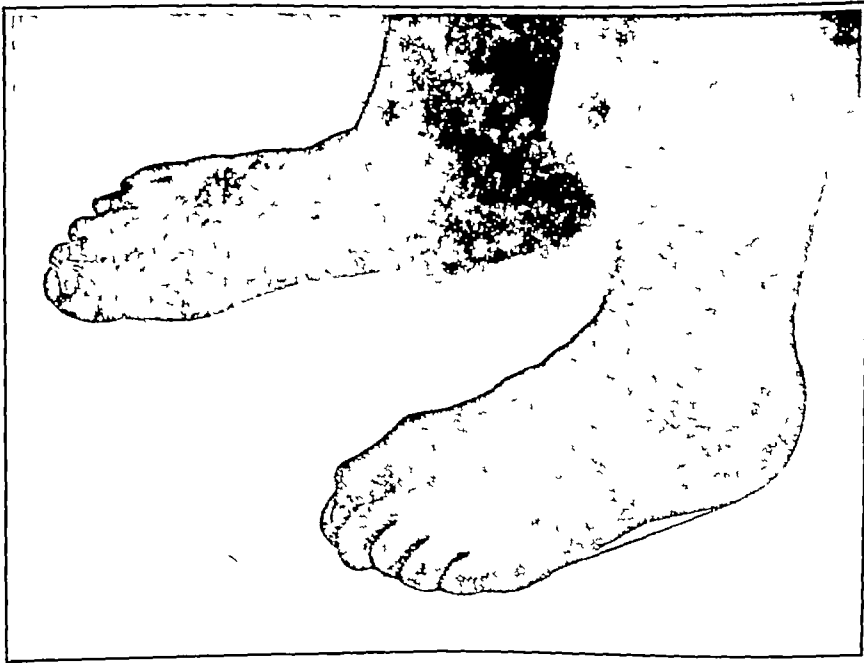


FIGURE 1 Photograph Showing the Spasmodic Hyperflexion of the Toes of the Left Foot

into this category. A spasmodic flexion of the toes was the presenting symptom. The successful relief of the condition by medication prompted the presentation of the case reported below.

Medication is often ineffective or unsatisfactory in the treatment of most of the muscular spasms and rigidities associated with disorders of the basal

ganglia. In the most frequent disease of the extrapyramidal pathway, Parkinson's syndrome, amphetamine (Benzedrine) sulfate, if given in sufficient dosage (20 mg or more), often diminishes the rigidity but has little if any influence on the tremor.¹ In some cases of spasmodic torticollis the drug is beneficial.² In my experience little or no benefit results from the use of amphetamine sulfate in dystonia athetosis, dystonia musculorum deformans or familial tremor of the head. It is my practice to

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F. J., a 20-year-old boy, was seen at the Out-Patient Department, Beth Israel Hospital, on March 3, 1942. There was no familial history of any neurologic disorder. The patient had had the usual childhood diseases, including mumps,

asles and scarlet fever. There had been no illnesses suggestive of encephalitis. In 1932 a large boulder weighing out 15 to 20 pounds was dropped on the left foot producing bruises and causing a limp for several days, but there were other ill effects. The patient had had jaundice in 1938. In 1939 he noted that the toes of the left foot flexed voluntarily, particularly while he was walking. This symptom was associated with a tired and tight feeling in the left leg and the thigh muscles. The involuntary movements of the foot gradually increased in severity and became continuous so that walking for more than a short distance became impossible. The patient had to discontinue work because of this disability.

Neurologic examination was negative except for the left foot. When the patient was in a standing position, the left toes were held in a state of marked hyperflexion so that the toenails — except that of the great toe — were completely hidden from view (Fig 1). Frequent slow spasmodic movements of the toes were present. Active extension of the toes was practically impossible, and passive extension was performed with difficulty. There was increased tone in the calf and thigh muscles. Walking was attended by great discomfort. All the deep reflexes were equal and lively, the left knee jerk being probably more active than the right. There was no Babinski reflex or ankle clonus. The sensory examination was normal. The cranial nerves were intact.

Examination of the spinal fluid disclosed clear fluid with an initial pressure equivalent to 95 mm. of water and normal dynamics. There were no cells. The total protein was 42 mg., the chloride 776 mg. and the sugar 96 mg. per 100 cc. The old-sol curve was 0000000000. Spinal-fluid Hinton and Kahn tests were negative. An x-ray film of the skull was normal.

The patient was given 30 mg. of amphetamine sulfate by intramuscular injection. Within $\frac{1}{2}$ hour a marked improvement in the muscular symptoms of the foot and leg occurred. The flexion spasm of the toes practically disappeared so that the patient was able to extend the phalanges almost completely. There was marked increased speed of movements of the toes. Walking became almost normal. The tightness in the leg and thigh disappeared. These effects of the drug gradually wore off over a period of 3 or 4 hours, with a return of the symptoms to their previous level. On the following day, to exclude the factor of suggestion, the patient was given an intramuscular injection of normal saline solution, which had no effect on the symptoms of the foot. Amphetamine sulfate

was then administered orally, in a dose of 20 mg. twice daily. To each 20 mg. of the drug, 30 mg. of phenobarbital was added, the latter sedative was also given at night to counteract the sleep-disturbing effect of the amphetamine sulfate.

On this medication marked improvement of the muscular symptoms has been maintained for forty-five months, so that the patient is able to walk long distances with little discomfort. There is an almost complete disappearance of the flexion spasm of the toes and of the feeling of tightness in the leg muscles. A residual mild hyperflexion of the toes remains. Omission of the amphetamine sulfate invariably results in recurrence of the symptoms to their previous level.

* * *

A case of spasmodic flexion movements of the toes is reported. This condition responded satisfactorily over a period of forty-five months to the oral administration of amphetamine (Benzedrine) sulfate.

It is recommended that patients who present symptoms suggestive of basal-ganglion origin be given an intramuscular dose (20 to 30 mg.) of amphetamine sulfate. If the symptom is beneficially influenced within approximately twenty minutes, the drug may then be taken orally in effective doses. Phenobarbital or another similar sedative may be prescribed with the amphetamine sulfate to counteract central overstimulation and may also be given at night to prevent the sleep-disturbing action of the latter drug.

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REFERENCES

- 1 Loman J, Myerson P G and Myerson A. Experimental pharmacology of postencephalitic Parkinson's disease. *Arch Neurol & Psychiat* 47:399-412 1942
- 2 Myerson A and Loman J. Amphetamine sulfate in treatment of spasmodic torticollis: report of 2 cases. *Arch Neurol & Psychiat* 48:823-828 1942

MEDICAL PROGRESS

OBSTETRICS

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THE following survey of the recent literature concerns significant developments in the management of various problems of obstetric practice

HABITUAL ABORTION

Habitual abortion continues to be one of the important problems facing the obstetrician. The study of the endocrine factors involved has offered a new approach of considerable value. Real progress has been made during the past year, with the result that a successful outcome can be obtained in certain pregnancies that would otherwise end in disaster.

All patients giving a history of two or more abortions should be thoroughly investigated. Thyroid deficiency, a frequent cause, should be checked by a test of the basal metabolic rate. General systemic disease should be ruled out. Pelvic tumors and other diseases should also be excluded. The general health of the husband, as well as the viability and morphology of the sperm, must be checked. If any abnormality is found in either partner, further investigation and treatment are indicated.

There are a large group of patients in whom no definite cause for abortion can be demonstrated. These patients may have normal fertility and yet may not be able to carry a pregnancy beyond two or three months. Among other attempts at treatment in these cases, many hormones have been tried, with little success. Progesterone, in particular, has proved a disappointment in most cases. Recently, a more scientific and hopeful approach has been made.

Vaux and Rakoff¹ have shown that a high percentage of habitual aborters exhibit a low pregnanediol titer and, even more frequently, diminished blood and urine estrogen levels. These findings indicate a hypofunction of the endocrine glands of pregnancy that may be due to the failure of the corpus luteum or the placenta. These authors have tried replacement therapy in a series of cases, with reported success. Their patients received 10 mg of progesterone and 10,000 rat units of alpha-estradiol benzoate two or three times weekly. The results are far more encouraging than those with progesterone alone.

Smith, Smith and Hurwitz² state that there is a low excretion of pregnanediol in patients experienc-

ing premature deliveries and intrauterine deaths. They have found the hormone titers in early pregnancy to be too varied to state a normal level. They were able, however, to cause a marked increase in the excretion of pregnanediol by the administration of large doses of diethylstilbestrol. Starting at the sixteenth week of pregnancy, with 30 mg of stilbestrol daily, they increase their dosage 5 mg weekly until a maximum of 125 mg a day is reached. This does appear to be a large dose, but it has been shown clinically that pregnant women tolerate stilbestrol much better than nonpregnant.

On the basis of this work, similar doses of the estrogens have been given, early in pregnancy, to habitual aborters. It was believed that since the estrogens increased the output of progesterone in the pregnant woman, progesterone need not be given. In many cases the stilbestrol was started before conception so that the pregnancy might begin with the proper hormone balance. Smith³ states that although this may prove to be the proper procedure, it may confuse the diagnosis of pregnancy, under this treatment patients will show an enlargement of the uterus, breast changes and other signs of pregnancy. Also, the therapy may cause a false-negative pregnancy test. Clinical results have been most encouraging, indicating a real improvement in the treatment of habitual abortion.

Hertig and Livingstone⁴ report on the pathological examination of 1000 cases of abortion. In this series the ova were anatomically normal in 26.6 per cent of cases. Considering all types of abortion, in which the fetus was otherwise normal, at the time of abortion, it is apparent from these figures that the pregnancy was essentially normal in 49.9 per cent of cases when the signs or symptoms brought the patient to the physician. From these figures it seems that the fetus in approximately half of all abortions has a possibility of being saved with proper treatment.

THE RH FACTOR

Among the recent developments in medicine, the Rh factor has become particularly important in the field of obstetrics. This factor is an antigen that, for all practical purposes, may be considered entirely similar to the A and B substances also found in the red cells. The Rh factor is present in about 87 per cent of white people, according to Diamond.⁵ It is the absence of this factor that is of significance

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Transfusion of Rh+ blood into an Rh— woman may cause an increasing hemolytic reaction, with the formation of antibodies. The factor exists only in red cells, and no anti-Rh antibody normally exists in human serum.

A woman with Rh— blood married to a man with Rh+ blood may have a fetus with Rh+ blood. In about one of fifteen such cases, the mother may be sensitized by one or more pregnancies. Once so immunized, the woman cannot be given a transfusion of Rh+ blood without danger of a fatal reaction. A single Rh+ transfusion to a non-pregnant woman with Rh— blood may initiate an antibody response. A subsequent pregnancy may cause erythroblastosis in the child.

In the pregnancy of an Rh— woman carrying an Rh+ fetus with an Rh+ father, the mingling of fetal and maternal blood is at first unimportant. In fact, since there is no direct mixing of the two bloods, some leakage must take place. During the first pregnancy, there is such slight admission of fetal red cells to the maternal system that only a small amount of antibody is formed. As a result, the first child is generally born in good health. The antibodies set up by the first pregnancy are retained by the mother and added to in succeeding pregnancies. In the second or third pregnancy the antibodies may reach sufficient concentration to enter the fetal blood and set up a hemolytic reaction. This may result in erythroblastosis in the fetus.

From a clinical point of view, it is essential that a careful history be taken on all pregnant women, first regarding blood transfusions and secondly concerning the presence of jaundice, anemia or stillbirth in any previous children. Should a positive answer be obtained to any of these questions, it is imperative that blood typing for the Rh factor be done. If the woman is found to be Rh— a further search for the presence of antibodies should be made.

It is also generally believed that all pregnant women should be typed for the Rh factor, even if they have had one or more normal children previously. If they are Rh— they may have been building up antibodies during the earlier pregnancies. Should the woman be found to have Rh— blood, a test for antibodies should be made about the twentieth week of pregnancy. If the test shows sufficient antibodies, labor should be induced as soon as possible, from the point of view of the safety of the infant. If the infant shows any sign of anemia or jaundice, a blood smear should be examined for evidence of erythroblastosis. If positive, a transfusion of Rh— blood should be given.

Blood of jaundiced infants of untyped mothers should be examined for evidence of erythroblastosis, and if the smear is positive, the infant should be given a transfusion of Rh— blood. Blood from the mother should not be used for transfusion to the child.

It is equally essential that an Rh— mother receive Rh— blood should a transfusion be necessary. This is important both from the danger of a transfusion reaction and from the danger of building up antibodies that might endanger the fetus in a future pregnancy.

Bouton⁶ states that Rh— mothers with antibodies in their blood should not nurse their children, since the antibodies may pass to the child through the mother's milk.

HEMORRHAGE

In the statistics of maternal deaths, a general improvement is apparent except in death from hemorrhage, indicating that sufficient advantage is not being taken of the greatly improved availability and simplicity of blood transfusion. It is also evidence that loss of blood during pregnancy, labor and post partum is not sufficiently checked. Too often, such observation is left in the hands of nurses or interns. Blood loss in obstetrics is difficult to judge. An experienced observer is necessary. This is the responsibility of the attending obstetrician and should not be delegated to others.

Gordon,⁷ in an excellent review of the causes of maternal death in Brooklyn, brings out the fact that in death reports the proper relation of hemorrhage to the cause of death is frequently omitted. He states that maternal death is often due to several causes rather than a specific one. In many cases of death from sepsis, the patient's resistance to infection has been severely damaged by excessive blood loss. There are other cases, such as cardiac failure, in which the final cause of death was precipitated by hemorrhage. Gordon reports that in Brooklyn, in 1943, a careful review of the maternal deaths showed that in 53 per cent hemorrhage was a significant factor. There were more deaths from hemorrhage than from any other cause, including toxemia and sepsis. It appears that the control and treatment of hemorrhage offer the greatest opportunity for a decline of the maternal death rate. Certainly, in many cases of death from hemorrhage, the patient could have been saved if the condition had been recognized early and proper treatment given.

Greenhill⁸ gives the following instructions for all women who bleed during the last few months of pregnancy. They should be sent to the hospital at once, without examination at home and without packing, except on rare occasions. They should be moved in an ambulance. On arrival at the hospital, determinations of blood type and Rh factor should be made immediately, if they have not been done previously. No rectal examinations should be performed. No vaginal examination should be done until the patient is in the delivery room, with sterile equipment for control of hemorrhage and rupturing the membranes. Further safety can be obtained by having the operating room set up for a laparotomy.

in case the vaginal examination starts free bleeding from a central placenta previa or other uncontrollable cause

The treatment of placenta previa is cesarean section in severe cases. In some cases of marginal previa in which the bleeding can be controlled by rupture of the membranes, the patient can be safely delivered from below. The use of a bag in this condition has largely been discarded. Williamson and Greely,⁹ in a description of a series of 162 cases from the New York Hospital, stress the fact that the operating room should be ready before examination. Central previa should always be treated by cesarean section. The best results were obtained from vaginal delivery when the bleeding could be controlled by rupture of the membranes. In a report of a ten-year study at the Sloan Hospital, Watson¹⁰ describes a maternal mortality of 11.5 per cent with the use of a bag against a maternal mortality of 3.4 per cent in cesarean section. The fetal mortality was 50 per cent with the use of a bag, and 4 per cent in cesarean section. With rupture of the membranes, the fetal mortality was considerably higher — 17 per cent — than with cesarean section. Watson also mentions some degree of shock in 63 per cent with the use of the bag.

In the treatment of abruptio placenta, conservative treatment or cesarean section may be employed. There is some difference of opinion in this matter. Gustafson¹¹ emphasizes the availability and use of large amounts of blood and plasma in these cases. He considers the ideal case for cesarean section to be an abruptio placenta of moderate degree, with the patient not in labor, or with labor not advanced, and with the fetal heart tones audible. In severe cases with a dead fetus, conservative treatment is often preferred. Conservative treatment includes rupture of the membranes, with small doses of pituitary extract to stimulate labor. Vaginal packing has not proved successful in controlling hemorrhage and is not in general use. The Spanish windlass is in the same category. Supportive treatment of the patient, including whole-blood transfusions, is extremely important. In many cases, even those with a dead fetus, if the cervix is hard and undilated, a cesarean section may be the preferable procedure. In any case of premature separation of the placenta, delivery from below may be followed by hysterectomy for hemorrhage. In the choice of procedure, as in all other types of hemorrhage, the therapy should involve the least possible shock to the patient and the best of supportive treatment, mainly the use of sufficient whole blood.

Rupture of the uterus is an obstetric emergency in which immediate diagnosis is imperative. The keeping of this possibility in mind is essential in diagnosis. Any patient with a previous cesarean section is in danger of rupture of the uterus. Lynch,¹² in a report from the Boston City Hospital on this problem, states that the prognosis is definitely influenced by the amount of time between rupture

and treatment. He considers most cases preventable, since they are due to either operative procedures or oxytocic drugs. He reports rupture following cesarean section as frequent and dangerous. All patients who have had previous sections should be carefully watched during the last few weeks of pregnancy. There is only one treatment for rupture — immediate hysterectomy. Large amounts of blood should be given freely. In patients who have had an internal version or a hard operative delivery from below, any sign of shock or internal bleeding should suggest rupture of the uterus.

In the treatment of obstetric hemorrhage, no one factor is of such help in improving results as the presence of a hospital blood bank. A great deal of time is saved. Also, if blood is easily available, it will be given in more cases. A description of the excellent blood bank at the Boston Lying-in Hospital is given by Irving.¹³

SEPSIS

Sepsis continues to be one of the important causes of maternal death, although statistics are improving. A large part of the present improvement must be attributed to new drugs. In spite of chemotherapy, however, women continue to have sepsis and continue to die from it. There is no reason for an increased confidence or feeling of safety in the attempt to eliminate the causes of sepsis. Much sepsis can be avoided and is due to factors that are preventable.

Septic abortion is, in the great majority of cases, due to artificial interruption of pregnancy. Poor asepsis, poor methods and unskilled hands are largely responsible. Self-induced abortion contributes a large number of these cases. In conjunction with the infection, there is usually considerable blood loss owing to incomplete emptying of the uterus. Also, the delay of patients in reporting to the hospital increases the risk. Many women wait at home until they are seriously ill before being seen. The treatment in these cases should be primarily conservative. When these patients are examined, any tissue protruding from the cervix may be removed, but the uterus should not be entered. Curettage should never be performed except for excessive hemorrhage. Since these patients have generally lost considerable blood, transfusions of whole blood should be given freely. Chemotherapy should be started in large doses. Fifty thousand units of penicillin every three or four hours up to 1,000,000 to 2,000,000 units is necessary. In my experience with 50 severely infected patients at the United States Naval Hospital in San Diego, none died under this regime. Five patients were curetted for hemorrhage, the remainder recovered without surgical interference. In the majority of cases the temperature fell to normal within forty-eight hours. Large amounts of blood were used in this series, no patient receiving less than one and some as many as six whole-blood transfusions.

Puerperal sepsis is well discussed by Douglas and Davis¹⁴ from the New York Hospital in a study of 600 patients with puerperal infection. Hemolytic streptococci were cultured in 90 per cent and aerobic streptococci were present in 70 per cent of their cases. Twenty-five per cent of the blood cultures from the operative deliveries in this series were positive, whereas cultures in only 8.5 per cent of the spontaneous deliveries were positive. Prophylaxis is most important in avoiding infection, careful asepsis in the delivery room being a prime factor. Patients should be watched carefully throughout pregnancy for anemia, since those with anemia have poor resistance to infection. Care should be taken during delivery and the third stage of labor to avoid any excessive loss of blood. Should excessive blood be lost, immediate replacement is indicated. Prolonged labor is a frequent cause of infection, and the increasing risk of infection in such cases should be well realized. Excessive trauma is one of the most avoidable causes of sepsis. Difficult deliveries, such as those by hard forceps and internal version, are fully as dangerous, from this point of view, as laparotomy, and because they often involve blood loss and shock, they should not be undertaken without consideration of these factors. In the application of forceps, skill and gentleness are essential, to avoid damage to the patient. Cesarean section should be done early before a patient is infected. Never should intraperitoneal section be attempted in the neglected or infected case, if delivery from below has been attempted, cesarean section is contraindicated. Avoidance of intercurrent disease is most important.

Douglas and Davis¹⁴ suggest the administration of sulfadiazine prophylactically during a prolonged labor as being of possible value in difficult operative deliveries but do not advise its use routinely.

The treatment of sepsis resolves itself into the primary factors of blood, fluids, nutrition and rest, all of which are of great importance. Sulfadiazine is of definite help in hemolytic-streptococcus and colon-bacillus infections. With the exception of colon-bacillus infection, penicillin is probably of more value. Whichever drug is used, treatment should begin early, with large doses, and should be continued for a sufficient length of time to be effective.

CESAREAN SECTION

Cesarean section continues to hold the attention of many writers. The problem of indications are widely discussed. Reviews of many cases continue to show the results of use and misuse of this operation.

Irving¹⁵ has published the results of ten years' experience with cesarean section at the Boston Lying-in Hospital in a series of 1887 cases, the incidence of cesarean section is given as 4.2 per cent, being twice as high among private patients as among those on the ward service. Operation was performed for dystocia in 71.6 per cent, for hemor-

rhage in 16.6 per cent and for other causes in 11.8 per cent. Irving states that midforceps delivery has proved as dangerous for the mother and eight times as dangerous for the fetus as cesarean section.

Pelvic delivery after a previous section was rarely done on the private service. Irving gives the following requisites for this procedure: the operation must have been done for a temporary indication, such as placenta previa, convalescence must have been afebrile, the procedure must have been performed by a competent surgeon, and after delivery from below the uterus must be explored for possible rupture. Following cesarean section, 78 women were delivered from below without rupture.

In the majority of cases of placenta previa the patients were delivered by cesarean section. Most cases of premature separation of the placenta were delivered by the pelvic route, particularly in the ablatio type. In only one eighth of the cases in which a diagnosis of premature separation was made were the patients delivered by cesarean section.

There was no difference in morbidity between the classic and the low-segment operation. The total morbidity for the series was 21.1 per cent, the total fetal mortality was 6.8 per cent, and the total maternal mortality was 1.3 per cent. There were 1 fatal case of peritonitis, 2 of hemorrhage and 3 of embolism. In all cases diagnosed as toxemia of pregnancy 2.7 per cent of patients were delivered by cesarean section.

Dieckman¹⁶ of the Chicago Lying-in Hospital, reports that statistics show that cesarean section can be performed with a mortality of 1 or 2 per cent in general hospitals and of 0.5 to 1 per cent in maternity hospitals. It is difficult to believe that the mortality must remain twice as high in general hospitals. Is this due to the presence of more intercurrent infection in general hospitals or to less well trained operators than in maternity hospitals? In 1922 the deaths after cesarean section were due to sepsis in 30 per cent, to shock and hemorrhage in 30 per cent and to toxemia in 19 per cent. Half to two thirds of these deaths were preventable. In 1931 five maternity hospitals performed cesarean sections in 6335 cases, with an uncorrected average mortality of 1.46 per cent. Realization of death from sepsis has prompted many obstetricians to an earlier use of cesarean section while the patient is still uninfected. This has caused some increase in incidence in the use of the operation but an absolute decrease in mortality.

Dieckman¹⁶ gives the following indications for cesarean section: obstructing tumors, contracted pelvis, with a true conjugate diameter of less than 8 cm and a transverse diameter of the outlet of less than 7 cm, a test of labor of twelve to eighteen hours in questionable cases being indicated — the pains should occur every two to five minutes, with a maximum of two rectal and two sterile vaginal examinations and with a deadline of twenty-four

hours for rupture of the membranes or labor, repeated cesarean section—a scar of the lower uterus is less apt to rupture than one from a classic section, but in view of the high maternal and fetal mortality from uterine rupture and the impossibility of knowing which scars will rupture, a previous section, in general, warrants a repeat operation, placenta previa, breech position in elderly primiparas or in patients with a contracted pelvis, transverse presentation in primiparas and recurrent transverse presentation in multiparas, and previous plastic operations

Dieckman¹⁶ considers cesarean section indicated in cases with an abruptio placenta with evidence of deep shock, low hemoglobin, a rapid pulse and an enlarged uterus or when dilatation of the cervix does not occur after the membranes have been ruptured for six to twelve hours

Free¹⁷ reports that cesarean section was performed in 500 consecutive cases at the Chicago Lying-in Hospital—an incidence of 4.43 per cent. There were 2 fatal cases, giving a mortality of 0.4 per cent, one death was due to cerebral hemorrhage or eclampsia, or both, and the other to hemorrhage and shock after a central placenta previa. The maternal morbidity, which was 31 per cent, definitely increased with the length of labor and with the rupture of the membranes

Waters¹⁸ recommends the use of extraperitoneal section in all infected and potentially infected patients. He reports extraperitoneal section in 250 cases, with maternal deaths in 2. Many of the operations were done for potential as well as for frank infection

There is no question that extraperitoneal section has a definite place in the hands of surgeons properly trained in this procedure. It is a reasonably complicated operation, however, and the peritoneum can easily be torn, thereby potentially infecting the peritoneal cavity. Hysterectomy following cesarean section in infected cases still has a valuable place in obstetrics. In this procedure the focus of infection is removed, and even though future child bearing is eliminated, a more rapid recovery with less residual pelvic disease can be expected

TOXEMIA

An excellent review of the toxemias of pregnancy has been published by Kellogg,¹⁹ who states the present situation of this disease with great clarity. "Little advance has been made in our understanding of the problem of hypertensive albuminuric pregnancy." He emphasizes the fact that the residual lesion after pre-eclampsia is invariably hypertension, with an incidence of 50.9 per cent, the incidence after eclampsia is increased to 60.8 per cent. Kellogg has never found glomerular nephritis in any patient as the result of eclampsia. The older the patient, the greater her pancy, the higher the blood pressure

during pregnancy, and the longer the duration of the illness, the greater the liability of the ultimate occurrence of hypertension. These factors are of extreme importance in the decision regarding treatment and the desirability of future pregnancies. It should always be remembered that the patient may have to pay in later years for an unduly prolonged pregnancy and that each succeeding pregnancy may add to this price

Kellogg recommends Veratrone as offering the fastest method of controlling convulsions in eclampsia. It also lowers the blood pressure in patients with pre-eclampsia who are on the verge of convulsions and thus greatly increases the safety of emptying the uterus. He states that this drug should be used in conjunction with magnesium sulfate. Veratrone will not save patients with severe eclampsia

The work of Smith and Smith²⁰ has shown that there are high levels of chorionic gonadotropin and low estrogen activity in the blood and urine of toxemic patients. There is also a deficiency of progesterone. This same situation occurs normally just before and during labor, and is in progress weeks before the development of toxemia. Fortnightly quantitation of serum gonadotropic hormone after the fifth month will demonstrate an abnormal rise in the level of this hormone eight to two weeks before the disease becomes clinically apparent in about 80 per cent of cases. The clinical application of this work has been most successful in pregnancy complicated by diabetes, in which the patients are particularly prone to develop toxemia

Hertig²¹ has developed a comprehensive view of toxemia of pregnancy that implies that many of its manifestations result from the same fundamental cause. He states that eclampsia, toxic separation of the placenta, cortical and pituitary necrosis and placental degenerations are all closely allied. A classification of separation of normally implanted placenta based on disease fixes the blame for mortality of this condition—almost, if not wholly—on the toxic variety. In proof of this statement, Hertig gives statistics to show that cases of toxic premature separation of the placenta treated by hysterectomy, rupture of the membranes, with or without vaginal packing, Spanish windlass or Pitocin show approximately the same maternal mortality—15 per cent

Some placental degeneration occasionally occurs in all cases grouped under the American classification of "hypertension of pregnancy," including "minimal toxemia," and prompt action can avert fetal death from this placental damage. With this placental degeneration the fetus may cease to grow. The smaller the baby, the more certain the presence of placental degeneration and the more important to remove the fetus from the uterus. These babies act their gestational age and are much better risks than normal premature babies of the same weight.

Cosgrove and Chesley²² state that the most significant and universal pathologic tendency in toxemia is definite functional and structural change in the vascular system, particularly the capillaries and arterioles. They point out that there is no general agreement regarding the existence of one toxemia of pregnancy, or whether a number of different causes may operate in the pregnant woman to give rise to a more or less similar group of manifestations. The only improvement in the treatment of toxemias is the average medical awareness of the potentialities for diagnosis and therapy in the earlier stages. Medical treatment should first be tried in all cases of toxemia of pregnancy, in patients who do not respond, termination of pregnancy is indicated. Cesarean section is recommended in culminating cases, but never after eclampsia has developed. The figures in 1625 cases of toxemia give a remote permanent hypertension in 53 per cent.

The most promising development regarding essential hypertension in pregnancy is the result obtained by the lumbodorsal splanchnicectomy of Smithwick.²³ In selected cases of young women with marked essential hypertension, this operation permits the patient to carry a pregnancy to a successful termination without damage to the vascular system. Fourteen patients with severe hypertension, relieved by operation, were successfully carried through pregnancy by Smithwick and Newell.²³ Of these, delivery was induced before term in 2 because of a developing toxemia. 1 case had a nontoxic separation of the placenta. These cases were of the type that ordinarily ends in disaster.

In conclusion, toxemia of pregnancy remains a disease of unknown etiology. Such improvement as has taken place in the incidence and treatment of this disease is due to its earlier recognition and to proper prenatal care. No specific curative treatment has as yet been found. Patients who do not respond to medical treatment should be delivered at the earliest possible moment by the simplest and least traumatic method. All women who develop this disease stand about a 50 per cent chance of subsequently developing a permanent hypertension. A long toxemic pregnancy, with repeated succeeding pregnancies, increases the incidence and severity of permanent hypertension.

ANESTHESIA

The addition of Demerol to the standard obstetric anesthesia with barbiturates has been well discussed by Irving²⁴ from experience at the Boston Lying-in Hospital. He reports that the combination of barbiturates with scopolamine obtains amnesia in 84 per cent of cases, whereas the barbiturates and Demerol result in satisfactory amnesia in only 70 per cent. The barbiturates and scopolamine have lowered the incidence of stillbirth and neonatal death, but there is some danger to the mother,

chiefly because of the possible appearance of edema of the lungs and other pulmonary complications during labor or delivery. This danger is avoided by the use of Demerol, which is rarely a respiratory depressant. The great advantage of the use of Demerol with scopolamine, instead of the barbiturates, is decreased restlessness during labor. So far as the effect on the fetus is concerned, Demerol is a much milder depressant. With barbiturates and scopolamine, only 62 per cent of infants breathe immediately, whereas with Demerol and scopolamine 82 per cent breathe at once. If the patient has become restless from the use of barbiturates, a shift to Demerol will greatly quiet her.

Much has been written concerning the use of caudal anesthesia in obstetrics. Hanley and Malone²⁵ report from the Los Angeles County Hospital on a series of 152 patients with no complications. They state that caudal anesthesia shortens the first stage of labor and prolongs the second, owing to the lack of the mother's voluntary expulsive power. The analgesia was successful in 96 per cent of cases. The single block is recommended as the most effective. Continuous caudal anesthesia requires the constant presence of a trained anesthetist, and many patients complain of backache following this procedure.

Andros and Henderson,²⁶ at the University of Michigan Hospital obtained complete relief of pain in 250 cases with continuous caudal anesthesia, without impairment of consciousness. There was no abolishment of voluntary motion or interference with uterine contractions. The respiration of the infant was not depressed, labor was shortened, and the blood loss was diminished. The incidence of operative delivery was definitely increased.

Hingson²⁷ presents statistics on caudal anesthesia in 42,000 cases. There were 7 maternal deaths due to misuse of the caudal analgesic, and 3 were regarded as anesthetic deaths. He states that complete block of the eleventh and twelfth thoracic roots gives complete relief. Uterine contractions continue if the analgesia does not go above the tenth thoracic root. Hingson believes that this anesthesia causes relaxation of the cervix by paralyzing the parasympathetic nerves. He recommends its use in toxemia, since it causes a definite hypotension.

Caudal anesthesia has definite possibilities in obstetrics, but it will probably not obtain general use at present. The difficulty of the technic as well as the danger involved if clumsily given, requires that it be used only by a trained anesthetist. The presence of an anesthetist for several hours during labor is not possible in the majority of cases.

Hellman and associates²⁸ report on the use of Pentothal Sodium. They claim that it should not be used for normal delivery and is indicated only in low-forceps delivery. They warn that the drug passes freely through the placenta, delivery should

therefore take place as soon as possible after the anesthetic has been given

In my opinion, spinal anesthesia, in the hands of a trained anesthetist, remains the choice for routine cesarean section. It is not only the most satisfactory for the operator but also appears to be the least upsetting for the patient. With the exception of occasional headache, it causes few postoperative complications.

THIRD STAGE OF LABOR

Aaberg and Reid²⁹ report on manual removal of the placenta at the Boston Lying-in Hospital. This series consisted of 217 cases, the incidence in all deliveries being 0.5 per cent. The chief cause was retention rather than hemorrhage. In this group there were 24 cases of placenta accreta. Prolonged labor was also an important factor in placental retention. The morbidity in this series was 28.8 per cent. The uterus was ruptured in 1 case. Four patients died following manual removal of the placenta, — 2 from infection and 2 from hemorrhage, — a mortality of 1.8 per cent. In 18 cases uterine tamponade was used, and the morbidity in these cases was 55.5 per cent.

This report emphasized, once again, the seriousness of manual removal of the placenta, which is a major obstetric procedure. Proper management of the third stage of labor is extremely significant. Attempts to express the placenta before it is fully separated are a frequent cause of excessive blood loss. Rough and careless handling of the uterus often starts hemorrhage. Excessive hemorrhage is the only indication for immediate removal of a retained placenta. Otherwise, it is better in the average case to wait at least two hours for a placenta to separate, since early interference may cause needless trauma and hemorrhage. A careful estimation of blood loss and the general condition of the patient permits the postponement of operative interference and frequently avoids it. Following delivery, the intravenous administration of Ergotrate hastens the separation of the placenta. Manual expression of the placenta should be avoided, if possible, until all signs point to a complete separation. If manual removal is necessary, a careful examination for placenta accreta should be made. If an accreta is found, no attempt at removal should be made — a hysterectomy is the only safe procedure.

PREGNANCY TEST

An additional pregnancy test has been developed that may well become a standard procedure. As reported by Robbins, Parker and Doyle,³⁰ it involves the use of the South African frog (*Xenopus laevis*). The great advantage of this test is its speed. It is easy to interpret and avoids the use of complicated histologic technic. It can be performed in any laboratory once the breeding and the care of the frogs can be satisfactorily accomplished. The reproductive life of the frog is ten to twelve years, and

they can be used repeatedly. After a positive test a frog may be used again in thirty days, and after a negative test, in five days. The test consists in the injection of an extract of urine into a female frog. In a positive test, the frog produces eggs within twenty-four hours, frequently, this takes place within eight hours. If no eggs are produced within twenty-four hours, the test is negative.

In a series of 100 cases there were no false-positive tests. There were false-negative reactions in 4 cases, 2 of which were tubal pregnancies and 2, early miscarriages, in these cases there was a low titer of the hormone. A larger amount of urine is now used in the test, with the result that there have been no false-negative reactions.³¹ It appears that the rat test is about six times as sensitive as the frog test. Although this makes no difference in normal pregnancy, in early and doubtful cases more urine must be used than is necessary in the rat.

REFERENCES

- 1 Vaux, N. W., and Rakoff, A. E. Estrogen-progesterone therapy: new approach in treatment of habitual abortion studies indicating its rationale in 24 treated cases. *Am J Obst & Gynec* 51: 353-366, 1945.
- 2 Smith, O. W., Smith, G. V., and Hurwitz, D. Increased excretion of pregnanediol in pregnancy from diethylstilbestrol with special reference to prevention of late pregnancy accidents. *Am J Obst & Gynec* 51: 411-415, 1946.
- 3 Smith, O. W. Personal communication.
- 4 Hertig, A. T., and Livingstone, R. G. Spontaneous, threatened, and habitual abortion: their pathogenesis and treatment. *New Eng J Med* 230: 797-806, 1944.
- 5 Diamond, L. K. Clinical importance of Rh blood type. *New Eng J Med* 232: 447-450 and 475-480, 1945.
- 6 Bouton, S. M., Jr. Rh factor — serologic background and clinical application. *Surg Gynec & Obst* 82: 743-748, 1946.
- 7 Gordon, C. A. Hemorrhage as most important cause of maternal death in Brooklyn. City of New York analysis of puerperal deaths of 1943. *Am J Obst & Gynec* 48: 557-564, 1944.
- 8 Greenhill, J. P. 1944 Year Book of Obstetrics and Gynecology 576 pp. Chicago: Year Book Publishers, Incorporated, 1945.
- 9 Williamson, H. C., and Greely, A. V. Management of placenta previa: twelve year study. *Am J Obst & Gynec* 50: 398-406, 1945.
- 10 Watson, B. P. Discussion of Williamson and Greely's.
- 11 Gustafson, G. W. Management of abruptio placentae. *Am J Obst & Gynec* 49: 103-113, 1945.
- 12 Lynch, F. J. Rupture of uterus. *Am J Obst & Gynec* 49: 514-511, 1945.
- 13 Irving, F. C. Blood bank for lying in hospital. *Am J Obst & Gynec* 51: 789-795, 1946.
- 14 Douglas, R. G., and Davis, I. F. Puerperal infection: etiology, prophylactic and therapeutic considerations. *Am J Obst & Gynec* 51: 352-371, 1946.
- 15 Irving, F. C. Ten years of cesarean section at Boston Lying-In Hospital. *Am J Obst & Gynec* 50: 660-680, 1945.
- 16 Dieckman, W. J. Cesarean section mortality. *Am J Obst & Gynec* 50: 28-48, 1945.
- 17 Free, E. G. Five hundred consecutive cesarean section operations. *Am J Obst & Gynec* 49: 401-408, 1945.
- 18 Waters, E. G. Use and abuse of cesarean section. *Am J Surg* 61: 208-212, 1945.
- 19 Kellogg, F. S. Toxemias of pregnancy. *Clinics* 4: 585-595, 1945.
- 20 Smith, G. V., and Smith, O. W. Endocrinological aspects: toxemias of late pregnancy: resumé of findings and conclusions. *Clinics* 4: 595-602, 1945.
- 21 Hertig, A. T. Vascular pathology in hypertensive albuminuric toxemias of pregnancy. *Clinics* 4: 602-614, 1945.
- 22 Cosgrove, S. A., and Chesley, L. C. Management and treatment of late toxemias of pregnancy. *Am J Obst & Gynec* 51: 67-74, 1946.
- 23 Smithwick, R. H., and Newell, J. L. Personal communication.
- 24 Irving, F. C. Advantages and disadvantages of barbiturates in obstetrics. *Rhode Island M J* 28: 493-495, 1945.
- 25 Hanley, B. J., and Malone, C. M. Caudal analgesia in obstetrics with special reference to repeated single blocks. *Am J Obst & Gynec* 50: 306-316, 1945.
- 26 Andros, G. J., and Henderson, C. W. Experience with continuous caudal anesthesia in obstetrics at University of Michigan Hospital: report of 250 consecutive cases. *Am J Obst & Gynec* 50: 69-74, 1945.
- 27 Hingston, R. A. Continuous caudal analgesia: interim report. *J A M A* 126: 1129-1131, 1944.
- 28 Hellman, L. M., Shettles, L. B., Manahan, C. P., and Eastman, N. J. Sodium pentothal anesthesia in obstetrics. *Am J Obst & Gynec* 48: 851-860, 1944.
- 29 Aaberg, M. E., and Reid, D. E. Manual removal of placenta: policy of treatment. *Am J Obst & Gynec* 49: 368-377, 1945.
- 30 Robbins, S. L., Parker, F. Jr., and Doyle, W. C. Use of South African frog (*Xenopus laevis*) in diagnosis of pregnancy. *New Eng J Med* 234: 784-787, 1946.
- 31 Parker, F. Jr. Personal communication.

SE RECORDS OF THE ASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

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CASF 33031

PRESENTATION OF CASE

A forty-three-year-old maintenance worker entered the hospital because of paralysis of the arms and legs.

The patient claimed to have been perfectly well until a week before admission, when he had a sudden onset of severe, cramping abdominal pains, with ten or twelve watery bowel movements during the day. He felt nauseated and vomited twice. No blood was noted in the vomitus, stools or urine. All the symptoms cleared on the following day. The patient felt well until three days before admission, when in the morning he was briefly conscious of a numbness and prickling sensation in both calves. That evening, he again complained of a severe sensation of "pins and needles" in both calves, lasting for half an hour. On the following day he first noted definite weakness, which made it difficult for him to rise from bed in the morning, and by 2 00 p m he was no longer able to stand. He believed that weakness had begun in the arms and legs at the same time, involving the distal muscles before the proximal ones, so that motions of the elbow and shoulder, knee and hip were retained after he was no longer able to move the fingers and toes. Forty-eight hours before admission he awoke with complete paralysis of the extremities, except for minimal motions at the shoulders and hips. He was unable to sit up in bed. He also began to complain of a moderately severe ache low in the back and of a slight ache in the arms and legs, but there was never severe pain in the extremities. The urine was noted to have a peculiar reddish-brown color, which it had never had previously, by the day of admission the color of the urine was again normal. There had been no weakness of the muscles of the face, dysphagia, dysarthria, respiratory difficulty, visual symptoms, sphincter disturbance, chills or fever. No drugs had been taken.

The past history was irrelevant except for mumps, measles, pertussis and diphtheria in childhood. The system review was negative, except as stated in the present illness. The patient's mother had died of abdominal sepsis. The father, six brothers and a

sister were living and well. There was no family history of infectious, degenerative, neoplastic or psychiatric diseases. The patient worked in a plant making rubberized cloth. No mention was made that other workers had had similar attacks, he was not known to have been exposed to toxic substances.

Physical examination revealed a complete, flaccid quadriplegia, except for slight elevation adduction at the shoulders, more on the right than on the left, and slight flexion and extension of the hips, also more on the right. No motions could be carried out against gravity. All motions of the neck were present, but there was weakness of flexion, so that the head could not be raised against gravity. The respirations were somewhat shallow, with some use of the accessory muscles. The rate was regular at 16 per minute. There was some contraction of the abdominal muscles, but weakness was marked. The patient was unable to maintain a sitting posture. There was complete areflexia including absent plantar responses. The only sensory abnormality was a questionable, minimal glove hypalgesia to just above the elbow. Light touch was intact, as were position and vibratory sensations.

The temperature was 98.6°F, the pulse 80, and the blood pressure 120 systolic, 80 diastolic.

Examination of the blood showed a hemoglobin of 15 gm per 100 cc and a white-cell count of 6600, with 75 per cent neutrophils and 18 per cent lymphocytes. The specific gravity of the urine was 1.025, and the pH was 4.5. There was a + test for albumin, and in the sediment an occasional granular cast was seen, although there were no white or red cells. The stools were guaiac negative. The initial pressure of the spinal fluid was equivalent to 130 mm of water. The total protein was 67 mg per 100 cc, and there were no cells. The gold-sol curve was 0001123311. The serum protein, sugar (fasting), calcium, phosphorus and phosphatase levels were within normal limits, as were the prothrombin time, the cephalin-flocculation test and an agglutination test with dysentery bacilli. An electrocardiogram and an electroencephalogram were normal. Stool cultures were negative for pathogenic organisms. Hinton tests of the blood and spinal fluid were negative.

On the day after admission there was no apparent change in the patient's condition. The vital capacity was 0.6 liter, the chest expansion was 0.5 cm. On the third hospital day a slight flicker of voluntary motion of the right patella appeared. At 10 00 o'clock that night the patient suddenly had respiratory difficulty, inability to swallow, marked accumulation of pharyngeal secretion and a weak voice, with loss of the higher pitches. There was no gag reflex. The facial and extraocular movements remained normal. He was placed in a respirator, and the pharynx was suctioned frequently. The bulbar signs subsided on the fourth day, but considerable respiratory difficulty remained. Outside the respira-

tor breathing was shallow, at a rate of 30 per minute. The electromyogram showed a low-voltage, repetitive discharge in the left and right extensor carpi radialis. This was also found in the left gastrocnemius muscle. These discharges were interpreted as similar to those seen in the neuritides.

Between the fourth and fifteenth hospital days the average temperature gradually rose from normal to 103°F. On the eighth day the urine became dark. On the ninth day there was fairly severe tenderness in the left lower quadrant and midline of the abdomen, without spasm. Peristalsis was normal. Marked signs of wasting were evident by the eleventh hospital day. A Levine tube was passed, and feedings were started. Penicillin therapy was begun on the next day, 15,000 units being given every three hours. On the thirteenth and fourteenth hospital days, livid, cool areas were noted on the arms and legs. On the nineteenth day there was a twenty-minute period of cyanosis, which began when the breathing became faster than the respirator impulses. Oxygen afforded improvement for several hours, but the patient suddenly became cyanotic and died.

DIFFERENTIAL DIAGNOSIS

DR. AUGUSTUS S. ROSE: No comment is made in the record concerning the mental status. I should also like to know if the blood pressure rose rapidly before death. I assume that the "dark urine" noted on the eighth hospital day was similar to that previously described.

DR. CHARLES S. KUBIK: There is not much said in the record about the mental state. Apparently, the patient was sufficiently conscious on admission to refuse intravenous medication. There are no further data regarding the blood pressure.

DR. MADELAINE BROWN: The mental state was normal, even when the patient was in the respirator.

DR. ROSE: In summary, this patient, without previous illness, developed a rapidly progressive motor paralysis involving the distal portion of the extremities first, then the trunk and neck and finally the muscles supplied by the medulla. It is peculiar, and I believe important to note, that paralysis of swallowing and difficulty in speaking improved after two days, although the respiratory mechanism remained impaired. The laboratory data showed normal routine blood findings and an essentially normal urine, except for the statement in the history that it was dark or dark red on two occasions. The total protein in the spinal fluid was 67 mg per 100 cc.

The symptoms, signs and course point clearly to a disease of the peripheral nerves. But the progression and the variability of the signs raise the question of central as well as peripheral involvement — suggesting the diagnosis of Landry's ascending paralysis. Landry's paralysis is not a specific entity but a condition that affects the lower spinal cord and fairly rapidly ascends to the medulla.

In this era of vitamins we must include vitamin deficiency in the differential diagnosis of any type of peripheral neuritis. In this case, however, there was no history of dietary deficiency or debilitating illness. The rapid onset and progression of the symptoms, as well as the variability of the paralysis, which I have mentioned, make vitamin deficiency unlikely. There was no history of ingestion of drugs or of contact with heavy metals. The abdominal pain raises the question of lead poisoning, yet in acute lead poisoning a different clinical picture is expected. On the other hand, infectious polyneuritis, or the Guillain-Barré syndrome, cannot be excluded quite so easily. This disease often appears following an upper respiratory infection or gastrointestinal upset. It frequently gives the picture of ascending Landry's paralysis, and some observers believe that there is involvement of the spinal cord and brain, as well as of the peripheral nerves. The spinal-fluid protein is elevated, without an increase in the cell count. Furthermore, in infectious polyneuritis it is not unusual to find motor paralysis with little or no sensory involvement. The diagnosis of infectious polyneuritis, however, does not give an explanation of the two striking and unusual features of this case: the abdominal pain and the two episodes of dark urine. These symptoms bring to mind the condition known as acute porphyria.

Acute porphyria is a condition that is probably congenital but may be acquired. It is of unknown etiology and is associated with episodes of dark or Burgundy-red urine due to an excess of porphyrin pigments and is often complicated by neurologic symptoms and abdominal pain. Last year Dr. Denny-Brown¹ published an excellent dissertation on the subject. He reported 2 cases, in 1 of which the patient recovered, the other patient died, and careful pathological studies showed spotty demyelination in the peripheral nerves and central white matter. Similar observations had been made by others. Dr. Denny-Brown, however, with his experience and observation on the effects of ischemia on the peripheral nerves, raised an interesting hypothesis concerning the pathogenesis of the neurologic signs in this disorder. Porphyrins apparently cause constriction or spasm of smooth muscle, as indicated by reported cases in which spasm of the colon was observed at operation and by others with constriction of the retinal arteries. Dr. Denny-Brown states that the pathological findings could be associated with ischemia due to intense arteriolar spasm. This is an engaging theory of the mechanism of symptoms but, of course, gives no clue to the etiology. Another article on the subject that should be mentioned is the monograph by Mason and others.²

Many of the patients in the reported cases of acute porphyria who died had had, prior to death, a severe delirium, coma and convulsions. Indeed, some patients who recovered had had such symptoms.

ce the disease occasionally occurs in several members of a family, we have a probable explanation for the inclusion of a negative psychiatric history in the record. Although the patient with acute porphyria may die in the first attack, many recover, and the recovery is usually complete.

I can make no other diagnosis in this case than acute porphyria with neurologic complications. It will be of interest to know whether tests for the detection of porphyrin pigments were done.

DR BROWN: Tests were performed and were positive. The interesting thing about this patient to me is that the spinal-fluid protein was increased.

DR ROSE: Yes, I should have mentioned that. In the cases reported in the literature the total protein of the spinal fluid was usually normal. I have no explanation why it was elevated in this case.

DR BROWN: Acute porphyria is the diagnosis that was made clinically.

DR ISAAC TAYLOR: Dr Kubik has asked me to say a few words about the condition known as acute idiopathic porphyria. The clinical features have been described by Dr Rose. When this patient came into the hospital the service believed, as Dr Rose did, that because of the neurologic findings, the dark urine and the abdominal pain, he was probably suffering from acute idiopathic porphyria, and the diagnosis was supported by the demonstration of a positive test for porphobilinogen in the urine. I might describe this test briefly. It has been observed that urine from patients suffering from acute idiopathic porphyria give strongly positive tests for urobilinogen with Ehrlich's reagent. The compound giving the red color with the aldehyde reagent is different, however, from urobilinogen in that it is insoluble in chloroform, whereas the red color produced by urobilinogen is easily soluble. Schwartz and Watson³ have studied these phenomena and have evolved therefrom a simple test that, when positive, is considered specific for acute porphyria. Ehrlich's reagent is added to urine from a patient with a suspected case, and the mixture is buffered with sodium acetate. If a red color develops, chloroform is added, and the mixture is shaken vigorously. The red color due to urobilinogen will be extracted quantitatively into the chloroform layer, if any red color remains in the aqueous phase, it is due to porphobilinogen and the test is positive. This is said to be a specific test for acute porphyria and is recognized as a simple method for testing for this condition. One should think of the diagnosis of acute porphyria in diseases characterized by atypical abdominal complaints, particularly cramps, nausea and vomiting, for which no organic lesion can be demonstrated. Nervous-system manifestations need not be present. The combination of abdominal pain and peripheral neuritis strongly indicates the diagnosis. The urine is ordinarily red during the acute attacks but not necessarily so.

This test affords a convenient way to demonstrate abnormal porphyrin compounds in the urine.

The mortality in cases of acute porphyria with neurologic complications is given in the literature as 50 per cent. We have seen 2 cases in this hospital during the past year, in both of which the patient died. As previously mentioned, one of Dr Denny-Brown's 2 patients survived.

CLINICAL DIAGNOSIS

Acute porphyritic polyneuritis

DR ROSE'S DIAGNOSIS

Acute porphyria, with neurologic complications

ANATOMICAL DIAGNOSES

Porphyruric polyneuritis

Bronchopneumonia

PATHOLOGICAL DISCUSSION

DR KUBIK: There is little or no question regarding the diagnosis of porphyria, which is established by the history and biochemical findings. There was bronchopneumonia, which was probably the chief cause of death.

In the peripheral nerves there were marked degenerative changes affecting a large proportion of the nerve fibers. Among these myelin sheaths were swollen, constricted, incompletely divided into short segments and, in many instances, broken up into rounded fragments. There were many fusiform enlargements and constrictions of the axis cylinders. In the spinal cord there was an axonal reaction of the anterior-horn cells. This change, consisting of a swelling of the cell and central chromatolysis of the Nissl substance, is secondary to disease of the axons of the cells peripherally and does not indicate primary disease of the spinal cord. It is, as a rule, a reversible reaction and does not lead to destruction of the cell.

The nuclei of the seventh cranial nerve were not remarkable, and I was unable to find a section of the medulla through the ventral nuclei of the tenth cranial nerves. There was no degeneration of myelin, and aside from the axonal reaction, no other lesion in the cerebrum, cerebellum, brain stem or spinal cord. The changes observed were those of a peripheral polyneuritis, there was nothing in the peripheral nerves or elsewhere that would enable one to make a diagnosis of porphyria. I do not know how to account for the neuritis or for the abdominal symptoms that are often observed in these cases.

REFERENCES

1. Denny-Brown D., and Sciarra D. Changes in nervous system in acute porphyria. *Brain* 68:116, 1945.
2. Mason V. R., Courville C. B., and Ziskind, E. Porphyrins in human disease. *Medicine* 12:355-439, 1933.
3. Schwartz, S., and Watson C. J. Isolation of uroporphyrin from feces in idiopathic porphyria. *Proc Soc Exper Biol & Med* 47:390-393, 1941.

CASE 33032

PRESENTATION OF CASE

A fifty-nine-year-old civil engineer was admitted to the hospital because of back pain.

The patient stated that he had occasionally had a stiff back all his adult life, but that the first incapacitating pain had occurred ten years previously. Strapping afforded sufficient relief to allow him to resume work. Eight years before entry he began to have pain in the lateral aspect of the right thigh, without associated back pain. This was noted while he was driving his automobile. The pain continued, and several months later a severe pain in the flank suddenly developed, immobilizing the patient in bed for about three weeks; he also developed a decubital ulcer. A physician told him that he had a "slipped" lumbar vertebra. Following this episode he was fairly well until three years before entry, when he again had moderate pain in the lumbar region requiring two or three days of bed rest. He subsequently had three or four similar attacks. Two years before admission he began having vague pain in the right hip and buttock, largely on motion or jarring of the right leg. Consultation with several physicians gave little benefit, and there was occasional extension of pain to the lower abdomen, associated with diarrhea. A barium enema gave normal findings. The teeth had been removed about seventeen months previously, without benefit. Several months later the patient had another attack of severe back pain and pain down the right thigh, requiring complete bed rest. He was seen by an orthopedic surgeon, who took x-ray films and advised a fusion, which was refused. A brace was applied, and the patient then stopped working for a year and went to the country, spending much time in bed. Six months before entry, while in a wheel chair, he rolled backward off a low porch, jarring his back. The resultant pain was so severe that he remained in bed for two weeks. For several months before admission he had stiffness and an occasional pain in the left shoulder. During the last two weeks he had noted pain down the lateral aspect of both thighs. He stated that this had never extended into the feet and that he had had no paresthesias; there was questionable numbness of the left anterior thigh, however.

On physical examination the patient experienced considerable difficulty sitting up in bed and getting into a standing position. There was marked limitation of flexion of the spine. Extension was restricted to about 5°, and lateral bending to about 20° either way, but without much lumbar motion. Tapping anywhere from the region of the third lumbar to the first sacral vertebra caused diffuse pain in the right buttock, but no point tenderness or deformity was noted. Straight-leg raising was possible to 70° on the left and 75° on the right, both limited by tightness of the hamstring muscles. Reflexes of the

knee and ankle were normal except for a slight increase of the patellar reflex on the right. There were no sensory changes. There was some limitation of abduction of the left shoulder. Examination was otherwise negative.

The temperature was normal, and the blood pressure 118 systolic, 65 diastolic.

Laboratory examination, including the red-cell count, the hemoglobin, the differential count, a blood Hinton test and the urine, was normal. The white-cell count was 11,700. The urine was negative for Bence-Jones protein. The total serum protein was 6.5 gm per 100 cc, with an albumin-globulin ratio of 2.0.

X-ray examination revealed a compression fracture of the third lumbar vertebra (Fig 1), with an extensive overgrowth of bone about the vertebral margins. There was definite irregular rarefaction throughout the collapsed body, and the intervertebral disks were preserved. There was no evidence of a paravertebral mass. There was slight anterior displacement of the body of the fifth lumbar vertebra on the sacrum, as well as a defect in the pedicles of the fifth lumbar vertebra. The abdominal aorta was calcified. The bones of the pelvis showed slight generalized decalcification but were otherwise normal. X-ray films of the skull, dorsal spine, ribs, femurs, left shoulder and chest and intravenous pyelograms were normal.

An operation was performed on the twelfth hospital day.

DIFFERENTIAL DIAGNOSIS

DR CHARLES S. KUBIA: The diarrhea was probably unrelated, but occasionally with lesions of the lumbar spine the pain is referred to the lower abdomen, even though that is above the level of lumbar dermatomes.

"The teeth had been removed about seventeen months previously, without benefit." It was not necessary to add the last part of that statement.

Apparently, there was some subjective sensory disturbance on the left side, most of the pain was on the right.

There was considerable discrepancy between forward bending or flexion and straight-leg raising. Forward bending and straight-leg raising are usually restricted to approximately the same degree. It is possible, I suppose, that the symptoms in this case were aggravated in the upright position and relieved by lying down.

The chief and only important symptom was pain. This was of the type caused by intraspinal disease in the lumbar region. The pain in the lower back in these cases is presumably a local effect, whereas that in the left side is referred pain, owing to compression or other involvement of the lumbar or sacral nerves. In the present case it is quite possible that all the leg pain was due to involvement of one pair of spinal nerves. There was no obvious weak-

s, sensory impairment or disorder of sphincter control to indicate involvement of the whole cauda equina, although some degree of such generalized involvement may have been present. Even with a large tumor of the cauda equina the neurologic examination is sometimes negative. It is quite possible that in this case lumbar puncture below the lesion or double lumbar puncture above and below would have revealed a subarachnoid block and increased protein at the lower level. But if there was no compression it was not severe enough to cause

of the body of the third lumbar vertebra, with the same bone destruction throughout the body and a considerable amount of overgrowth of new bone about the margin. The x-ray appearance is definitely that of a pathologic fracture, but the new bone formation is rather unusual for a malignant tumor.

DR KUBIK: That is not exactly what I expected to see. Would you say that these are congenital defects at the fifth lumbar vertebra?

DR LINGLEY: I think that there was some dispute about that. But usually such a lesion is con-

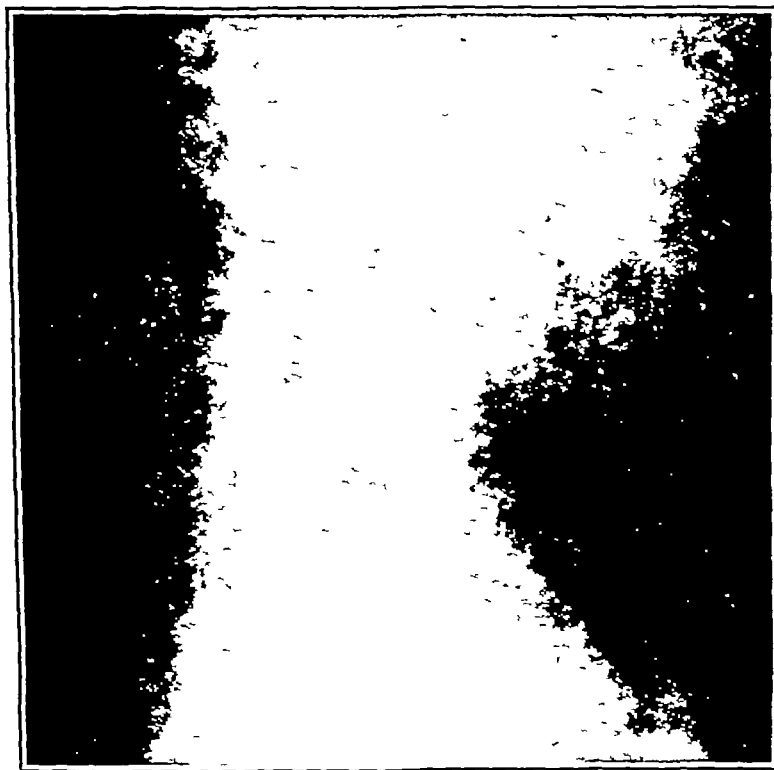


FIGURE 1

any obvious impairment of function. X-ray examination revealed a compression fracture of the third lumbar vertebra, since the character and distribution of the pain described fit a lesion at that level and in the absence of any better alternative lead, I assume that the fracture was responsible for the symptoms.

May we see the x-ray films?

DR JAMES R. LINGLEY: These films, taken at another hospital about ten months before admission here, show the slight anterior displacement of the body of the fifth lumbar vertebra, as well as some compression of the lateral border of the third lumbar vertebra with a break of the cortex at that point. In the lateral view there is bone destruction throughout the vertebral body. These films taken in this hospital, show a well marked compression fracture

considered to be congenital. It may be traumatic but is likelier to be congenital.

DR KUBIK: When I went over the clinical summary I supposed that the defects and anterior displacement of the fifth lumbar vertebra were probably due to spondylolisthesis, that condition might explain the early attacks of stiffness of the back, which were probably not related to the attacks of severe low-back and leg pain that began ten years before the patient entered the hospital. Those could be explained by the fracture of the third lumbar vertebra so that one must think of a condition that had existed over a long period and finally resulted in a pathologic compression fracture. I had in mind a hemangioma which is a frequent tumor of the vertebrae and often asymptomatic but which occasionally results in symptoms without fracture. I

thought that the hypertrophic changes were the result of superimposed trauma and did not indicate an osteoblastic type of tumor

A comparison of the two sets of films shows that a marked change had taken place in a comparatively short time. It seems to me that there is too much destruction for hemangioma. I suppose that I shall have to revise my opinion to include a more malignant type of tumor, but the character of the symptoms had been essentially the same for a period of ten years, that fact certainly indicates that they were being caused by the same condition all that time. Other tumors that might occur in this locality

chondroma, osteochondroma, chordoma, giant-tumor and perhaps osteoid osteoma. Chordoma may be a slowly growing tumor and may, I suppose, be a possibility. Myeloma, which may occasionally be a solitary lesion, is another possibility. I recall a case in which the diagnosis was made by Dr. Holmes from the x-ray findings and in which symptoms had existed for eight years, some x-ray treatment has been given and may have prolonged its course. The case under discussion today was a tumor of some kind, but I am not able to say exactly what.

DR. TRACY B. MALLORY: Have you an opinion, Dr. Sosman?

DR. MERRILL C. SOSMAN: It looks like a central tumor in the vertebra. I believe that the important approach is to determine the point of origin, whether primarily in the spinal canal, with secondary erosion of the bone, or primarily in the bone and secondarily involving the canal. I think that the latter is more probable from the x-ray appearance. The most frequent of these is the giant-cell tumor, which of course may last for many years, or a solitary myeloma. The original films show erosion of the pedicle on the right side. This pedicle is missing on the right side of the third lumbar vertebra, and the

adjacent lamina and articular processes are destroyed, so that it is invading the surrounding portion of the spinal canal at that point. Giant cell tumor may do that, as well as solitary myeloma.

DR. JOSEPH S. BARR: I think that we ought to add tuberculosis to the list of diagnostic possibilities. Central tuberculosis of bone in adults may remain in a semiquiescent stage, with mild symptoms for a long period, producing hypertrophic changes, not only in the spine but also in the knee. I do not know that that is the diagnosis, but I should like to raise the possibility.

DR. GRANTLEY W. TAYLOR: No one mentioned metastatic carcinoma, which is by all odds the most frequent cause of such a destructive lesion in bone.

DR. LINGLEY: I interpreted these films and put myeloma first, chordoma second and hemangioma third.

CLINICAL DIAGNOSIS

Tumor of third lumbar vertebra

DR. KUBIK'S DIAGNOSIS

Tumor of third lumbar vertebra

ANATOMICAL DIAGNOSIS

Chordoma of third lumbar vertebra

PATHOLOGICAL DISCUSSION

DR. MALLORY: The operation on this patient was exploratory for the purpose of biopsy to establish a diagnosis. A destructive lesion of the vertebra was found, and the biopsy showed the characteristic histologic picture of chordoma. These are often slowly growing tumors for a long time, but then they may suddenly pick up more rapidity of growth and extend widely in a comparatively short period.

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

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MATERIAL should be received not later than noon on Thursday two weeks before date of publication

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COMMUNICATIONS should be addressed to the *New England Journal of Medicine* 8 Fenway Boston 15 Massachusetts

WHAT IS EPIDEMIC DIARRHEA OF THE NEWBORN?

RECENTLY the Committee on Problems of the Newborn Infant of the District of Columbia Section of the American Academy of Pediatrics¹ described epidemic diarrhea in the following manner

An infant in the neonatal period who previously well, suddenly passes one or more very loose or liquid stools combined with sudden abnormal loss of weight (after the period of initial weight loss) or one of the other symptoms associated with this type of diarrhea, such as vomiting, listlessness, drowsiness, refusal of feeding, short feeble cry, pallor or elevation of temperature, should be immediately isolated and reported to the hospital authorities as a suspected case of infectious diarrhea

The committee further recommended that should similar symptoms develop in another exposed in-

fant, both the suspected case and the new case should be reported to the health department as cases of infectious (epidemic) diarrhea. The decision whether the suspected case should be reported was the responsibility of the health department

Although recognition of this syndrome during the course of an epidemic is a fairly simple matter, the diagnosis of the first or even the second case often presents considerable difficulty. Infants are peculiarly subject to diarrhea, which may be caused by a large variety of conditions. The lack of knowledge regarding the etiology of epidemic diarrhea of the newborn adds to the confusion that obscures diagnosis in the individual case. For this reason most health departments have hesitated to include epidemic diarrhea of the newborn among the reportable diseases. In Massachusetts the problem is still further complicated because of a law that requires local jurisdictions, under certain circumstances, to assume financial responsibility for the care of persons ill with diseases declared reportable by the Department of Public Health.

If epidemic diarrhea of the newborn were declared a reportable disease, a thorough inspection of each nursery in which a case or a suspected case had appeared would have to be made by the proper health authority, otherwise it would be pointless to report the disease. Because of the large number of cases of diarrhea that occur among newborn infants, this would throw a sizable burden on health agencies. Furthermore, investigations would have to be instituted in many cases in which the diagnosis would prove to be incorrect. Perhaps a more logical control program would consist of periodic inspections of all hospital nurseries to ensure that institutions providing care for the newborn were operating according to standard procedures. Since in Massachusetts the Department of Public Health has been empowered to license hospitals, including those with maternity wards, this agency has the authority to make such inspections.

Investigation of several outbreaks of epidemic diarrhea of the newborn, as reported elsewhere in this issue of the *Journal*, has revealed many inadequacies in the care of the newborn in those hospitals where outbreaks occurred. In several hospitals overcrowding in the nursery, insufficient personnel, im-

proper making of formulas and faulty sterilizing technics emphasize the need for greater diligence on the part of those responsible for the care of newborn infants. Laboratory examination of so-called "sterilizing solutions," nipples and other utensils used in the nursery frequently showed heavy bacterial contamination. The presence of Group D streptococci in the noses and throats of infants ill with epidemic diarrhea suggests that these babies had been exposed to organisms normally found in the human intestinal tract. *Salmonella* infection of the newborn, three outbreaks of which have been reported in Massachusetts,² is further evidence that because of poor technics in the nursery infants are exposed to intestinal pathogens. In a recent investigation of *Salmonella* infection on a pediatric ward, it was found that individual thermometers were not available for each patient.³ Cultures of these thermometers after they had been "sterilized" revealed bacterial contamination. Similarly the vaseline used as a lubricant on the thermometers was also contaminated. Such faulty procedures provide ready means of transmitting infection from infant to infant.

Although infant mortality rates have declined considerably, neonatal death rates have remained fairly stationary. In a state like Massachusetts where the great majority of births occur in hospitals, it is obvious that the problem of neonatal mortality is intimately associated with events in such institutions. A recent report by Frant and Abramson⁴ indicates that the persistently high incidence of mortality among the newborn in New York City is due, in a great measure, to diarrheal disease. They found a steady rise from 1926 to 1936 in deaths due to diarrheal disease during the neonatal period.

It is apparent that, because of the large number of births that take place in hospitals, the matter of adequate infant care must be the direct concern of each administrator. Proper supervision of nursery technics and formula-making methods should be routine practice in all hospitals. Periodic inspections by health departments, including conferences with nursery supervisors on infant care, would constitute a real contribution toward the solution of this problem. Such a program would be a more practical and useful preventive measure than the routine

reporting of all cases of suspected epidemic diarrhea to the local health department.

REFERENCES

- 1 News and notes. *J Pediatr* 27:391, 1945.
- 2 Rubenstein, A. D., Feemster, R. F. and Smith, H. M. *Salmonellosis as public health problem in wartime*. *Am J Pub Health* 34:811, 1944.
- 3 Massachusetts Department of Public Health. Unpublished data.
- 4 Frant, S., and Abramson, H. Epidemic diarrhea of newborn, epidemiology of outbreaks of highly fatal diarrhea among newborn babies in hospital nurseries. *Am J Pub Health* 28:36-43, 1938.

URBAN STAKE IN RURAL HEALTH

THE status of health and medical services in rural communities is not in itself a responsibility of physicians living and practicing in cities, although members of the medical profession in all areas regret the fact that adequate medical care appears to be beyond the reach of a large segment of the population and wholeheartedly approve of conscientious and workable plans to remedy the situation. The matter concerns urban physicians, however, when proposed legislation to improve medical facilities in rural areas is intimately related to the practice of medicine throughout the United States, it is the duty, as well as the privilege, of the medical profession to give the closest attention to all such proposals. An example of this type of legislation is afforded by certain provisions of the Wagner-Murray-Dingell Bill, which are designed to make the Bill palatable to organized farm groups.

This is not to deny that improvements in rural public health and medical practice are needed or to minimize the efforts of physicians all over the country to investigate the problem and recommend a solution. At the first annual meeting of the National Conference on Rural Health, the inadequacy of public-health departments in rural areas, the high maternal and infant mortality in those areas as compared with the cities and the lack of well trained physicians in the small towns received close attention.¹ The medical profession was urged to sponsor and participate in plans to extend the benefits of prepayment medical care to people in the country. It was recognized that the problem involved is both economic and social, as well as professional, and the need for the establishment of health centers and for public-health education in rural communities was emphasized. It was also recommended that the kind of experiments envisioned in the proposed national

health legislation be limited to circumscribed areas the unfavorable experience with compulsory health insurance in Rhode Island being cited. The conference represents the determination of organized medicine to take active leadership in the movement to improve rural health and medical practice.

An encouraging aspect of the recent hearings on the Wagner-Murray-Dingell Bill was the farmer's opposition, as expressed by a spokesman for the National Grange, to the suggested extension of federal authority without the opportunity for the general public to express its opinion.² Of further interest is the fact that the Grange suggested means for remedying the deficiencies of rural health that are compatible with those favored by organized medicine. For once, the appeal to a special and powerful group contained in a bill that is a catchall for every scheme to improve medical care at the expense of individual freedom and initiative appears to have missed its mark. But the activity of the medical profession is still vital. In the words of Dr F S Crockett, chairman of the Committee on Rural Medical Service of the American Medical Association, "It is our duty to exercise the greatest vigilance wherever we believe our common interests are threatened through federal domination. There can be too high a price paid for help."¹

REFERENCES

1. National Conference on Rural Health. *J A M A* 131:553-561, 1946.
2. Wagner-Murray-Dingell Bill, hearings on S. 1606 — to provide for national health program. *J A M A* 131:683-692, 1946.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

CHEEVER — Clarence A. Cheever, M.D., of Boston, died December 31. He was in his eighty-ninth year. Dr. Cheever received his degree from Harvard Medical School in 1885. Until his retirement in 1921, he practiced in Milton. A collection of historic microscopes was organized at Harvard Medical School largely through his efforts. A son, Dr. Austin W. Cheever of Boston, survives.

KERRIGAN — Joseph H. Kerrigan, M.D., of Stoneham, died January 3. He was in his sixty-second year. Dr. Kerrigan received his degree from Tufts College Medical School in 1907. He was a former president of the Middlesex East District Medical Society and was a fellow of the American Medical Association. For twenty-five years, he was chairman of the Board of Health in Stoneham. His widow, two daughters and a son survive.

TOZIER — Charles H. Tozier, M.D., of Winchester, died January 1. He was in his seventy-second year. Dr. Tozier received his degree from Harvard Medical School in 1901. His widow and a sister survive.

A HUNDRED YEARS AGO

Dr S. Brown of Wilmington, Massachusetts, reports that some atmospheric peculiarity prevailed in the summer and autumn of the past year which had an uncommon influence on the biliary organs of persons in his vicinity. Sporadic instances of icterus have made their appearance more or less every year, but the jaundice as an epidemic, until the summer and autumn of last year, had never to his remembrance met his observation. In some instances the disorder was complicated with typhus fever, but in more, the organs merely concerned in the digestive process suffered the effects of disease and gave evidence of local derangement. The symptoms in different individuals were nearly similar. At the commencement of the disease, a chilliness took place, with soreness about the gastric region on pressure, accompanied with flatulence and febrile symptoms, the urinary discharges were scanty and resembled bloody water from first to last, the skin began to show a slight yellow tinge, which progressed to an orange color in a few days more, when it began to assume a more natural color, and at the end of two or three weeks, the patient would resume his customary occupation if his disease was not complicated by typhus. The disease prevailed on both sides of the Merrimac as far up as Manchester, and probably farther, and whether it was solely endemic to the region of the Merrimac is a question he would like to have answered. The disease had the appearance in several instances of being contagious, but a contagious jaundice would be an anomaly. To what this disease may be attributed, there are various conjectures, whether to a state of the atmosphere, a deficiency of water in wells, or to the stagnant waters of the reservoirs connected with the lakes at the head branches of the Merrimac, let off to supply the factories below, is a question. He has had some suspicions that the last might be productive of a peculiar miasma which would specifically induce a diseased state of the biliary organs, because the water from these reservoirs was green and slimy, indicating its stagnated condition. — The whole number of deaths in Boston during the past year by the published General Abstract, was 3389, or 804 more than the year previous, of which 1472 were children under five years of age, over sixty years, 254. The number of deaths from consumption is put down at 485. With a population of 120,000, the mortality of Boston during the last year would thus be 2.82 per cent. — Influenza is prevalent at Bangor, Maine. In Baltimore it is also severe, and has even extended as far as New Orleans. — Dr. Kimball, of Lowell, amputated the hand of a young man who had been severely injured by a picker, the other day, having previously administered the letheon. The patient declared that he had not experienced the slightest degree of pain by the operation. — The special attention of medi-

cal gentlemen in the country is called to the regulations of the Massachusetts General Hospital in the admission of patients. The institution is admirably conducted, and may without hazard of contradiction be called the first hospital in America — The Vermont Medical Society has appointed Drs Charles Hall, C W Horton, A G Dana and Dyer Storer as its delegates to the National Medical Convention in May next — Dr Alexander E Hosack, of New York, has twice permitted the experiment of administering the ethereal vapor by Morton's apparatus, as preliminary to surgical operation, during the last week. The first case was an amputation of the thigh, the other case was the removal of a scirrhus testis which had acquired a formidable size. Both these patients testify to the entire unconsciousness which resulted from the inhalation, while the effects lasted — The Secretary of this Commonwealth makes a report annually to the Legislature of all the births, marriages and deaths which have been returned to him from the city and town clerks, and such other officials as are authorized to make these returns. No one believes the document to be just what it should be in point of completeness. We can only express a hope that this matter will finally receive that attention which its importance merits, both from the people of Massachusetts at large, and those whose duty it is to collect the information and transmit it to our indefatigable Secretary of State — Not long since, a public meeting was held in Boston to devise ways and means for providing the poor people of the crowded metropolis with better and cheaper tenements than they now have. One curious fact is apparent, viz that some of the poor seem to prefer dark, unventilated houses to better places. We most heartily pray that something may be done at once to better their state — One of the neatest things of the day has been sent abroad by Messrs Ticknor and Co of this city, entitled, "Memoranda for Young Practitioners in Midwifery, by Edward Rigby, second American edition, enlarged and improved."* Lilliputian as it is in its dimension, there are sixty-two closely printed pages of excellent material, which give correct information in the fewest words. We opine that a series of such miniature treatises, embracing medicine and surgery, that might be carried without inconvenience in a fob, would not only sell readily, but also be very much prized. Some who are always too busy to study large tomes, thus armed with accurate homoeopathic doses of professional knowledge, would perhaps have in their pockets more than they ever had in their head — Extracted from the *Boston Medical and Surgical Journal*, January, 1847

R F

*The Harvard Medical School copy of this Lilliputian miniature is inscribed "D. D. Slade from Prof W. Channing, Jan 1st, 1847. Slade then a medical student subsequently became professor of applied zoology."

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

NEW MOBILE UNIT FOR THE BLOOD PROGRAM

The Massachusetts Blood Donor Program of the Division of Biologic Laboratories will begin to operate a second Mobile Unit some time in February. With only one unit, the collection of blood has had to be limited to approximately one hundred pints per day. Another unit will make it possible to handle two hundred pints daily. Both units will be available to operate five days each week. If full schedules can be maintained for these units, present estimates indicate that fifty thousand pints of blood can be collected, processed and distributed during 1947.

At the beginning of the program the quota for each community was established at one donation for each 150 persons in the community. This quota has not proved sufficient to meet the demand, especially for whole blood, therefore it will be necessary to increase the annual quota of cities and towns participating in the program. New quotas will be raised to approximately one donation for each 100 residents.

Before the Mobile Unit visits a community, a representative of the Department of Public Health outlines the program to members of the local Red Cross chapter and interested social and civic organizations. Physicians and hospital authorities are urged to attend such meetings and to take an active part in the program. They are also invited to see the Mobile Unit in operation at any nearby location, and are welcome to visit the new blood-processing laboratory at the Division of Biologic Laboratories in Forest Hills. Staff physicians at the laboratory will be glad to discuss technics, the clinical application of blood products, the integration of state and community blood-procurement facilities or any other phase of the program.

MOBILE UNIT SCHEDULE

The Mobile Unit of the Massachusetts Blood Donor Program will make the following visits in the near future

PLACE	DATE
New Bedford	January 27, 28, 29
Stoneham	January 31
Quincy	February 3, 4
Concord	February 5
Cambridge	February 13, 14

BOOK REVIEWS

Dietotherapy: Clinical application of modern nutrition. Edited by Michael G. Wohl, M.D. With a foreword by Russell M. Wilder, M.D., Ph.D. 8°, cloth, 1029 pp., with 93 illustrations. Philadelphia: W. B. Saunders Company, 1945. \$10.00.

Here is a textbook almost certain to achieve popularity. It concerns nutrition, now a large cinder in the public eye. It is written by many authors, each an authority in the

particular compartment of nutrition that is his bailiwick. Each chapter is put together in a precise fashion, and a useful bibliography is appended. On the whole, therefore, any reader can easily plough through the whole field of nutrition and can dig deeply where he chooses. He can learn of everything from the normal diet to what is known of calcium and phosphorus metabolism, he can approach the vitamins in alphabetic sequence, or he can acquire up-to-date information regarding diet therapy whether it be for diabetes or in surgery, to make thin people fat or fat people thin, or influence the allergies or anything else.

The typography and illustrations are excellent. Best of all is the editing. For, despite the multiplicity of authors and subjects, the editor has succeeded in making each chapter read as if it had been written by himself, and hence as a whole the volume flows smoothly as though from a single pen. The book is highly recommended to students and practitioners for reference or steady use or even for the pleasure of reading a lively medical book on a topic that is currently of great general interest.

Rypins' Medical Licensure Examinations. Topical summaries, questions and answers. By Walter L. Biering, M.D., M.R.C.P. (Edin., hon.) With the collaboration of a review panel. Fifth enlarged edition. 8°, cloth, 546 pp. Philadelphia: J. B. Lippincott Company, 1945. \$6.00.

Dr Rypins published the first edition of his standard work on examination questions in 1933 under the title *Medical State Board Examination Questions*. Successive revisions were issued in 1935, 1937 and 1939.

The author was secretary of the New York State Board of Medical Examiners for fifteen years, and his original book and its revisions, constituting four editions, were based on a critical survey of thousands of questions actually used throughout the United States. Typical questions were selected and appended to the general review of the various subjects.

The work covers the whole field of medicine, including the basic disciplines, the specialties and general practice. Each section is preceded by a review of the subject under consideration. These reviews, which are well written and succinct, emphasize the important points of each subject. Technical procedures have been omitted.

After the death of Dr Rypins the editorship of a new, enlarged edition was intrusted to Dr Biering, who is well qualified to carry on the work, since he is secretary of the Federation of State Medical Boards of the United States and a member of the National Board of Medical Examiners.

The fifth edition carries out the original plan of separate summaries for each subject, with a selection of typical questions. The review sections were prepared by authorities in their fields. A new section on pharmacology has been added in recognition of the growing significance of this subject. Naturally, it is assumed that the candidates are adequately trained in the medical sciences, and therefore no attempt is made to teach them anything new.

A careful study of medical examinations in the United States indicated a general agreement among examiners regarding the material essential for candidates, and the present volume adheres closely to this groundwork.

The preliminary chapter, entitled "The Philosophy of Examinations" is an interesting review of the history of examinations in the United States and Great Britain.

The National Board of Medical Examiners is an important organization whose certificates are accepted by forty-five states and two territorial boards in lieu of the regular licensing examinations, as well as by the boards of England and Scotland for admission to the final practical examinations of these boards.

The text throughout is printed with a good, large type on soft paper, permitting extended concentrated study without visual fatigue.

This book is recommended as a reference source for all medical and public libraries.

Men under Stress. By Roy R. Grinker, M.D., and John P. Spiegel, M.D. 8°, cloth, 484 pp. Philadelphia: The Blakiston Company, 1945. \$5.00.

This book, coming up for review after the acute emotional emergencies of war have subsided, must be considered from two perspective planes. First, from the standpoint of the authors, the text material was composed in the heat of battle

to the accompaniment of pressures and directives from higher headquarters. The senior author, a neuropsychiatrist and psychoanalyst of no small professional stature, was subjected to conditions that threatened the ego of many if not all the psychiatrists in the service — not by life-or-death exigencies, but by constant subjugation to the inevitable regressively constituted elements of the military service. Adjustment to this set of circumstances resulted in the massive amount of productive energy that rolled this book and *War Neuroses* through the presses. The reviewer can personally recall similar vicissitudes so that the emotional tensions evoked by reading this book produce a sympathetic "me too."

From the standpoint of the content, the recounting of general psychiatric principles, even the rapid-fire disposition of the acute combat traumas that unleashed latent inflammable emotional reactions, the reviewer found ambivalent pleasure in reading and in identification. There are fairly comprehensive descriptions of the background and specific emotional stresses in aerial combat work, as well as of the various types of direct and late reactions noted in flying personnel. The use of Pentothal "narcosynthesis" (for effecting an abreaction of repressed traumatic material and then re-establishing ego-environmental integration via the imposition of the therapist as a kindly yet authoritative paternal symbol) was the chief therapeutic plan described. The reviewer regards this as another military emergency procedure substituted for more thoroughgoing psychotherapy.

The fluent, persuasive and authoritative style of the text may lead many readers to believe that when emotionally ill military personnel were released from the authors' care they were for the most part able to be returned to duty (only 2.3 per cent of the officers and 21.9 per cent of the enlisted men reportedly had to leave the service). The reviewer and many of his colleagues stationed at different convalescent or other hospitals in the Zone of Interior were frequently consulted about patients who had been under the authors' care at "The Don" and had been returned to duty — only to be separated from the service for formidable psychiatric disabilities. Not a few of these patients had been so imbued with the ritual of the "fiak juice" by contacts with other Don Cesar matriculants that they admitted to various entirely conscious expressions and outbursts delivered purely for the benefit of the therapists. This is not related in any derogatory manner, since similar occurrences punctuate any psychiatric practice, but for the record. Another item concerning flying personnel should be documented. A number of youngsters undertook flying training because the preliminary training period lasted in many cases for nine months or more before the trainee even sat in an airplane. Another several months elapsed before permanent assignment after wash-out. Consciously or unconsciously, a year or so before actual combat work took place, rather than the emulation of Icarus, was an important motivation in applying for this training.

The psychiatrically oriented reader at this date will find this book interesting and somewhat instructive. In the psychiatrist who was involved in the treatment of combat casualties considerable ambivalence may be provoked.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Extremities. By Daniel P. Quiring, Ph.D., head of the Anatomy Division, Cleveland Clinic Foundation, and associate professor of biology, Western Reserve University, Beatrice A. Boyle, artist, Cleveland Clinic Foundation, Erna L. Boroush, M.A., fellow, Anatomy Division, Cleveland Clinic Foundation, and Bernardine Lufkin, A.B. 8°, cloth, 117 pp., with 105 illustrations. Philadelphia: Lea and Febiger, 1945. \$2.75.

The purpose of the diagrams in this manual is to make clear to students the origin, insertion, action and arterial and nerve supply of the muscles of the upper and lower extremities, together with their motor points.

Modern Urology for Nurses By Sheila M Dwyer, R N, B S, director, School of Nursing and Nursing Service, Southampton Hospital, Southampton, New York, and George W Fish, M D, associate professor of urology, College of Physicians and Surgeons, Columbia University, New York City. With a foreword by Helen Young, R N. 12^o, cloth, 287 pp., with 66 illustrations. Philadelphia: Lea and Febiger, 1945. \$3.25.

This second edition of a standard manual for nurses has been revised throughout to provide for the advances in medical knowledge occurring since the publication of the first edition. The use of penicillin and the sulfonamides in the treatment of urinary infections has been included, and the sections on ureteral transplants have been greatly expanded, new material on the diagnosis of the treatment of cancer of the prostate has been added. In this edition an attempt has been made to place greater emphasis on the patient as an individual. The concluding chapter on a teaching program for urology has been completely rewritten, and the outline has been set up in question form.

The Yearbook of Psychoanalysis Volume I. Sandor Lorand, M D, managing editor. 4^o, cloth, 370 pp. New York: International Universities Press, 1945. \$10.00.

The first volume of this yearbook contains contributions from twenty authors dating back to 1942. This beginning date was chosen because it was considered advisable to republish some of the studies on war neuroses appearing prior to 1945. In the future, only current contributions will be published in the annual volumes. The papers are by eminent writers in the field of psychoanalysis and are mostly reprinted from other publications. They are brought together in one volume, however, for convenient reference. The first paper is a reprint of an English translation of Sigmund Freud's remarks on the theory and practice of dream interpretation, first published in 1923. This volume should be in all large medical libraries and in special libraries of neurology and psychiatry.

Prescribing Occupational Therapy By William R Dunton, Jr, M D. 8^o, cloth, 149 pp. Springfield, Illinois: Charles C Thomas, 1945. \$2.50.

This is a partial, revised edition of a book first published in 1928 and long out of print. A new chapter on rehabilitation has been added, and the references to the literature have been brought up to date. This brief text should be useful to all interested in the subject.

Annual Report of the Baruch Committee on Physical Medicine for the Fiscal Year April 1, 1944, to March 31, 1945. 8^o, paper, 82 pp. New York: Baruch Committee, 1945.

This first annual report of the Baruch Committee gives in detail reports from the teaching and research centers and the projects in physical medicine supported by grants from the committee. Twelve institutions were recipients of these grants. Seven million dollars was allotted for fellowships in physical medicine, and five fellowships were granted. The total disbursements for the fiscal year ending March 31, 1945, for research and fellowship grants amounted to \$1,111,250.

Our Inner Conflicts: A constructive theory of neurosis By Karen Horney, M D. 8^o, cloth, 250 pp. New York: W W Norton and Company, Incorporated. \$3.00.

In this monograph Dr Horney has offered new viewpoints on the neuroses. It is written not only for psychiatrists but also for those interested in applying psychoanalysis to education, social work and anthropology and for the layman opposed to psychoanalysis.

A History of Medicine By Douglas Guthrie, M D, F R C S (Edin.), F R S E. With an introduction by Samuel C Harvey, M D, William H Carmalt Professor of Surgery, Yale University School of Medicine. 8^o, cloth, 448 pp., with 72 plates. Philadelphia: J B Lippincott Company, \$6.00.

This is a short authoritative history of medicine, written in a pleasing style that is easy to read. Each chapter concludes with a list of books for further reading on the subjects discussed. Appended to the text is a classified bibliography of medical history.

Nursing and Nursing Education By Agnes Gehlman, R A, A M, professor of nursing and chairman of the Skidmore College Department of Nursing, New York Post-Graduate Medical School and Hospital. 8^o, cloth, 72 pp. New York: The Commonwealth Fund, 1946. \$1.00.

In this short monograph the author briefly discusses the development of nursing as a profession in the United States, beginning with the opening of schools of nursing in Boston, New York and New Haven in 1873 and of public health nursing in New York in 1877. Chapters on nursing supply and demand before and during World War II, personnel policies in the maintenance of standards, nursing education and the estimated nursing supply and demand in the post-war period follow. The monograph is issued under the auspices of the Committee of Medicine of the Changing Order of the New York Academy of Medicine. It is well written, and the material well organized. It should be considered a part of the study of medical care as a whole. It should prove of interest to all who are concerned with medical care and health, as well as those professionally engaged in nursing and nursing education.

Dr W C Röntgen By Otto Glasser, Cleveland Clinic Foundation. 8^o, cloth, 169 pp. Springfield, Illinois: Charles C Thomas, 1945. \$4.50.

This popular short biography of Röntgen is well written and covers the various periods of his life from his school years until his death in 1923. Naturally most of the text is devoted to the period, 1895 to 1897, when he made his remarkable discovery of the x-ray. Medical students should be encouraged to read this small book, which should be in the collections of all public and university libraries.

Profitable and Necessary Book of Observations By William Clowes. With introductions by De Witt T Starnes, professor of English, University of Texas, and Chauncey D Leake, M D, dean, School of Medicine, University of Texas. 8^o, cloth, 232 pp. New York: Scholars' Facsimiles and Reprints, 1945. \$6.00.

This reproduction of an early English imprint should be in all medical libraries. It includes Clowes's treatises on gunshot wounds and syphilis. There are also two short observations by G Baker on preserving dead bodies for a long time and on the nature and properties of quicksilver.

General and Plastic Surgery with Emphasis on War Injuries By J Eastman Sheehan, M D. 8^o, cloth, 345 pp., with 496 illustrations. New York and London: Paul B Hoeber, Incorporated, 1945. \$6.75.

This book presents operative technics for every part of the body, with emphasis on plastic surgery. The text, which is well printed on good paper and profusely illustrated, is followed by an adequate index.

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PROGRAM

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Interatrial Block. A case report. Dr Richard A Bloomfield.
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(Notices continued on page xvii)

The New England Journal of Medicine

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Volume 236

JANUARY 23, 1947

Number 4

CARE OF THE PATIENT BEFORE AND AFTER OPERATION*

With Special Reference to Fluid Requirements and the Importance of the Weighing Scale in Evaluating the Status of Hydration

OWEN H. WANGENSTEEN, M.D.†

MINNEAPOLIS, MINNESOTA

THE subject assigned to me has to do with the safe conduct of the patient through his operation. And if all the answers to all problems bearing on such an issue were available to the surgeon undertaking an elective operation, his course of action would unquestionably be altered in many circumstances. The items that assure safe conduct of a patient through the hazards of an operation might well be discussed under the following three headings: the preparation of the surgeon, the preparation of the dissection and the preparation of the patient and his care after operation.

The adjudication of the element of risk alone is an item of great importance not only to the surgeon but also to the patient who assumes the risk.

PREPARATION OF THE SURGEON

A realistic approach to the appraisal of risk is obviously necessary and involves not only the item of whether the patient has been prepared adequately for the procedure but also the matter of whether the surgeon's preparation has been adequate. Surgical specialty boards affect to be able to determine what surgeons are proper persons to operate for the relief of certain surgical disorders. And already in consequence of the work they are doing, a noticeable improvement has become discernible in the quality of surgical practice — an impetus that will gain momentum with the years. Yet there are considerations of an intangible nature, relating to the surgeon's preparation, that have an important bearing on the outcome of an operation and are not readily susceptible of analysis. Has the surgeon scheduled more operations than he can conveniently do in the

time he has allotted himself? Will he be hurried by prior commitments or appointments that may deter him from carrying out the plan of procedure with the usual care? A recital of such considerations and similar problems familiar to every surgeon can be embarrassing, it is perhaps best that I pursue the inquiry no further. It is to be remembered that surgeons are not immune from the trials of other mortals.

The following words of Portia in the *Merchant of Venice* on such matters are well known:

If to do were easy as to know what were good to do, chapels had been churches and poor men's cottages princes' palaces. It is a good divine that follows his own instructions. I can easier teach twenty what were good to be done than be one of the twenty to follow mine own teaching.

The qualities of which the surgeon stands in need have been enumerated as "an eagle's eye, a lady's hand and a lion's heart." However far these gifts may go in developing a good surgeon, they are not enough for the difficult surgical tasks of today unless that surgeon is fortunate enough to possess a sturdy pair of legs. Co-ordination of hand and mind is a vital requisite of precise and well performed surgery. Intentness of purpose, complete absorption in the problem at hand and a devoted consecration to his task — these are qualities that help the surgeon to dispel the fatigue and weariness of long and strenuous operative ordeals. There are times, indeed, when the surgeon appears to stand in need of special postoperative treatment: there are operations that tax the surgeon's endurance as much as the patient's ability to withstand them. But as the *Bible* tells us, "The sleep of a labouring man is sweet" and after a night of repose and rest — among the greatest of life's blessings — the surgeon returns refreshed to his labors.

Convalescence without complication is ordinarily synonymous with a well executed operative pro-

*Presented at the annual meeting of the Massachusetts Medical Society, Section of Surgery, Boston, May 23, 1946.
†From the Department of Surgery, University of Minnesota Medical School.
This study is based on research supported by grants from the Graduate School, the Augustus L. Searle, Dr. and Mrs. Harry B. Zimmermann, Dr. Berenice Montanary and Robert A. Cooper Funds for Surgical Research.
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(Notices continued on page xvii)

Pulmonary lobectomy provides an example. This operation was being done for bronchiectasis twenty-five to thirty years ago with an appalling mortality. Today, the same operation is being done in experienced hands in many places with a mortality of 1 per cent or less. Churchill, of this city, was the first to indicate that this potentially formidable procedure could be done at a risk comparable to that for excision of the acutely obstructed but unperforated appendix. This is an accomplishment of no small order. Yet all the essential items involved in the successful performance of this operation were known when the pioneers in the field were making their initial skirmishes with the problem. Now, however, the true significance of the pertinent knowledge relating to the problem has become known to the right persons. It takes time for the meaning of minor differences not apparent on first acquaintance with a problem to be appreciated. In other words, experience has been a great factor in reducing the mortality of pulmonary lobectomy from 50 to 1 or 2 per cent.

There were good surgeons twenty-five years ago, but surgical organization in well appointed hospitals is more efficient today. Anesthesia is considerably better, as is the knowledge of care of patients before and after operation. Surgeons have learned that it takes time and patience to do an operation well, and elimination of hurry by the surgical team has played an important role in the reduction of mortality. Improved nursing care has also been a factor.

Similar progress has been made with many operative procedures. Primary resection of the colon gave way to the exteriorization operation because the surgeon of that day was not ready for primary resection. Today, with a keener appreciation of the elements that are essential for the success of the procedure, well trained surgeons perform primary resection for cancer of the colon with a mortality of 5 per cent or less.

Experience

No less a person than the late Dr Harvey Cushing put considerable emphasis on the item of experience. In the fall of 1928, I had occasion to spend a week on the stand in his operating room at the Peter Bent Brigham Hospital. Each day he operated for a brain tumor. I marveled at his dexterity and nicety of technic and the facility with which he decided where the tumor was and what area of brain tissue should be excised. On leaving his clinic, I took occasion to thank Doctor Cushing for permitting me to sit in the stand day after day and watch him operate. I asked what the criteria were by which he decided so readily the area and extent of the excision of brain tissue. I was only partially prepared for his answer "Experience." I then asked if that experience could be resolved in terms of a definition. Dr Cushing replied again, "Experience." I countered by saying that in a case of breast tumor,

such characters as size, hardness and attachment to the skin helped the surgeon to determine the nature of the lesion. I asked if there were any parallel so far as brain tumors were concerned? Dr Cushing became a bit impatient with my impertinence and said again, "Experience." In the fall of 1934, Dr Olin West, secretary of the American Medical Association, gave an address at the Wisconsin State Medical Association Meeting at Green Bay, Wisconsin, in which he stated that Dr Harvey Cushing had emphasized the great value of experience in clinical medicine and had written an article on the subject. Failing to find the article in the *Quarterly Cumulative Index Medicus*, I wrote to Doctor Cushing. He appeared to have remembered the occurrence of 1928 and treated me somewhat more indulgently than when I had accosted him after a long and arduous operation. Although he denied having written philosophically concerning the importance of experience, Dr Cushing said, "If I spoke of experience, I undoubtedly spoke of technic." The intervening years have confirmed in my mind the truth of his emphasis on the great value of experience.

PREPARATION OF THE PATIENT

The customary technic of preparation of a patient for operation twenty-five years ago consisted essentially in giving a cathartic before operation and in repairing anemia by the transfusion of blood. With the resolution of the mystery that surrounded the cause of death in experimental pyloric and high intestinal obstruction by Gamble and his associates^{1, 2} in 1925, light and understanding came into the problem of fluid requirements of patients. During the twenty years that have elapsed, surgeons and other medical specialists have gradually been aroused from their apathy regarding the fluid and electrolyte requirements of patients. Collier and his associates^{3, 4} at the University of Michigan, for a period of many years, have been emphasizing the importance of evaluating daily the fluid and electrolyte requirements of surgical patients when the administration is parenteral. It is not long since, in many hospitals, when the fluid given parenterally to any patient was 0.9 per cent saline solution, whether or not glucose was included in the infusion. The hazard of the practice is not difficult to foresee, especially in an older age group of patients, in whom oliguria occurs more readily than in young robust persons. For every 6 gm of sodium chloride retained, approximately a liter of water is retained. When patients receive 18 to 27 gm of sodium chloride (2 to 3 liters of saline solution) a day and when their daily requirements, even in the early postoperative phase when abnormal losses must be covered, lie somewhere between 4.5 and 9.0 gm a day (0.5 to 1 liter of 0.9 per cent saline solution), it is understandable that difficulties arise with the maintenance of fluid and electrolyte balance. In

cedure Critical self-analysis with reference to the surgeon's responsibility for the occurrence of complications is the only rational attitude for the surgeon to assume. A surgeon who is Pollyannish in his attitude to his own accountability for postoperative complications shuns the growth and improvement that result from self-criticism and self-censure. Moreover, there are additional complications, such as thrombophlebitis, embolism, coronary thrombosis and cerebral hemorrhage, for which the surgeon is not strictly accountable, in that they are essentially unavoidable. Unfortunately, no absolute criteria are available to indicate whether or no these complications will occur, although in assuming certain operative risks, the surgeon is fully aware that he is overstepping the borders of convention in his anxiety to bring hope and relief from suffering to his patient.

PREPARATION OF THE DISSECTION

In any operation, preparation of the surgeon is important and implies a satisfactory preparation of the dissection — probably the most vital of all considerations in the safe conduct of a patient through an operation. Although the question of what or whose operation was done is significant, more important still for the immediate success of the procedure is *how* the operation was done. Nice anatomic dissections taking advantage of the knowledge of tissue planes, the careful dissection of blood vessels with minimal loss of blood, the precise placement of sutures and the gentle handling of all tissues — these are the items that ensure the immediate success of an operative procedure and the recovery of the patient. If, on conclusion of the operation, the surgeon is convinced that the objective of the operation was met satisfactorily and that the procedure was in accord with good physiologic principles, the ultimate success of the operation affords real promise of attainment.

No amount of excellent preoperative and postoperative care can make up for an operation that was badly done.

Fortunately, the emphasis on speed is rapidly disappearing from surgery. In another generation the heedless, reckless surgeon who is constrained to emphasize the element of hurry above every other consideration will have disappeared from the scene. And surgery will be the better when, in the memory of active surgeons, such meaningless claptrap phrases as "get in quick and get out quicker" have been completely forgotten. Perhaps we should begin by deletion of the word "theater" as the place where operations are done, operations have ceased to be spectacles, and they are dramatic only so far as they succeed.

The year 1946 marks the centennial of the first public administration of an agent to make operations painless and the coming of the beautiful word "anesthesia" by the medical poet, Oliver Wendell

Holmes. Relief from pain during a surgical ordeal — what a gift to humanity! Improved techniques of anesthesia, as much as any other consideration, have made it possible to eliminate the element of hurry in operations. The co-ordinated effort of anesthetist and surgeon can make an operation simulate physiologic sleep. There is much yet to be desired in the waking and recovery periods to make them less of a nightmare to the patient. Will the time ever come when an operation will be described as an experience not unlike a pleasant dream? We must of necessity be realists, nevertheless, this is a goal toward which surgeons should turn their eyes.

The use of dry sponges and the weighing scale constitutes an expedient that affords the surgeon satisfactory orientation concerning the extent of the blood loss at any juncture of the operation. To supplant, in kind and in amount, the fluid lost during operation serves to spare the patient the ill effects of protracted lag intervals in therapy.

One factor that bears on the success of operations cannot be stressed too much: deliberate thought and wise planning beforehand. This factor has to do with lessons learned and sometimes painfully in the process of critical self-analysis by realistic surgeons — perhaps best described as practical wisdom, an item on which I shall have more to say presently.

The Synthesis of New Facts

How does it happen that the surgery of today in certain fields can accomplish things that, in the light of the achievement of twenty-five years ago, must be considered no less than miraculous? To be certain, we of today have some new facts at our disposal. And a new fact can change the whole complexion of a problem. New facts, however, are surprisingly few. How many books contain a single new fact? The great impetus to medicine and surgery that comes from a few isolated key facts is astonishing. A general improvement in the tone of practice may be observed: witness what boons to medicine the sulfonamides and penicillin have been.

When the present accomplishment in a given field is compared with that of twenty-five years ago, the gain from the synthesis of known facts is appreciated. This circumstance is encouraging and should serve as a stimulus to all to ferret out from the scientific catacombs of libraries facts that, if known to the person who should be in possession of them, save endless labor and frequently supply the information necessary to the solution of a problem. It does, however, take experience and orientation to profit by reading and study in the interphases of one activity with other specialties. And for many, such vagrant rumination turns out to be wool gathering. Hence, the value of discussion groups such as this. The important thing is for the unknown knowledge to come into the hands of the person who is striving to effect the synthesis.

fluctuations in weight exceeding 3 per cent of the cooperative normal value suggest the necessity for closer scrutiny of the situation

Apart from patients with pneumonia, peritonitis and distention, from whatever cause, in whom the problem of fluid and electrolyte balance is often difficult, the predicament sometimes presents itself unexpectedly in patients who, in spite of a slow convalescence, were believed to have been progressing satisfactorily. The difficulty may be one of overhydration or dehydration. Neglect of weighing such patients is usually responsible for the delay in recognition. Yet, sometimes, especially in patients with complications such as distention, the situation develops so insidiously that the threatening difficulty of gains or losses in weight is not appreciated in time to avert the results of such fluctuations

Dehydration and electrolyte loss A loss of 5 to 6 per cent of the body weight, in consequence of abnormal fluid losses, is usually accompanied by recognizable clinical signs of dehydration and hypochloremia. If an inadequate amount of sodium chloride is given and 10 per cent glucose is injected intravenously, a liberal urine output may follow, and dehydration ensues in a few days if this electrolyte loss is not made up. If the fluid loss, responsible for the decrease in body weight, was occasioned by vomiting or suction applied to an intubated duodenal tube, alkalosis will usually follow, owing to a larger loss of the chloride than the sodium ion. In cases in which losses of intestinal secretions from the lower reaches of the bowel, as in diarrhea, are accountable for the contraction in weight, acidosis may occur. In either event, if no renal damage has occurred, saline solution is ordinarily a satisfactory repair agent, as Gamble⁶⁻⁸ has indicated.

Coller and Maddock⁴ suggested that dehydration and electrolyte loss be treated with saline solution, 0.5 gm of sodium chloride per kilogram of body weight being given for a depression in the plasma chloride of 100 mg per 100 cc below the normal value of 560 mg. It has been our practice in this clinic to proceed somewhat more cautiously, not giving nearly so much sodium chloride as is suggested in the Coller-Maddock rule, awaiting manifest evidence of diuresis before attempting to bring the plasma chloride value up to normal. Coller and his associates⁵ recently emphasized the so-called "salt intolerance" of sick surgical patients and characterized that clinical rule as "highly inaccurate and dangerous."

Zintel, Rhoads and Ravdin⁹ have employed 2 per cent solutions of ammonium chloride intravenously in the correction of alkalosis, believing that restoration of glomerular filtration will be quickened thereby. In the correction of severe acidosis a sixth molar sodium lactate solution¹⁰ or a 5 per cent solution of sodium bicarbonate may be used to restore the normal buffer values in the blood.

Overhydration Increases in body weight of 3 to 6 per cent may be unaccompanied by symptoms except edema. In old patients, whose physical status is poor, pulmonary edema, pneumonia and heart failure may result from too generous administration of sodium chloride. Not infrequently, when oliguria occurs in such patients accompanying the retention of water, the plasma chloride may remain low. Efforts to elevate the plasma chloride to a normal value by the administration of added sodium chloride intensify the difficulty. The usual initial provoking cause of the abnormal water retention and gain in weight in these patients is administration of more sodium chloride than the patient requires. Moreover, sodium chloride retention appears to occur in pneumonia¹¹ and in peritonitic states accompanied by intestinal distention. And, owing to impaired glomerular filtration,¹² severe oliguria may be present despite the fact that the body weight is above normal. In such cases, when the weight is 4 to 6 per cent or more above the initial normal level, I have contented myself with the slow intravenous administration of 800 to 1000 cc of a 50 per cent glucose solution a day, giving enough glucose to meet the basal caloric needs. The recovery from pneumonia, pulmonary edema and heart failure in such patients following the correction of the overhydration is often remarkable. There are mortality and morbidity of treatment, as well as of the disease process. And it is important to attempt to know which is which. When diuresis commences in such oliguric edematous patients, following fluid and sodium chloride retention, lesser concentrations of glucose with larger amounts of water may be given. For patients who have become oliguric or anuric because of renal damage from sulfonamide administration or a transfusion reaction, the dialysis of retained urea through the peritoneum by perfusion appears to be promising.¹³

Many of the situations that Jones and Eaton¹⁴ described in their excellent paper on nutritional edema were undoubtedly due to the excessive administration of sodium chloride. And whereas this agency, together with hypoproteinemia, may be a likely theoretical causal factor in bringing about obstruction at the efferent outlet after gastrojejunal anastomoses, I consider this item far less significant than overinversion of tissue by the surgeon in the making of the anastomosis.¹⁵ Early dismissal of patients from the hospital after gastrointestinal anastomoses of every kind is contingent on the making of satisfactory anastomoses that do not obstruct. It is time that surgeons appreciate that they themselves, in making imperfect anastomoses with overinversion of tissue, invite obstruction at the new stoma.

The Weighing Scale

Its accuracy in evaluating hydration For more than six years, in our clinic, the weighing scale has

this connection, it is not out of place to point out too that Collier and his associates,⁵ in 1944 revised downward their estimates of sodium chloride needs in the ordinary surgical patient

The Patient in Good Physical Condition

A patient who enters the hospital for a gastric resection for ulcer or carcinoma who is unobstructed and whose hemoglobin is 12 gm or better and who has been eating well and has not lost weight needs no special preparation for operation. A careful preoperative diagnostic study, inside or outside the hospital, including evaluation of the patient as an operative risk, is obviously indicated. The same principle holds generally, in my experience, for all conditions that come within the purview of the general surgeon. There are those who insist on several days of preoperative hospitalization, during which succinylsulfathiazole is given to patients expected to undergo resection for cancer of the colon. My thought and practice is to make every effort to effect a satisfactory anastomosis, a single row of interrupted silk sutures sufficing for any anastomosis from the stomach to the rectum. My experience has been that no intestinal antiseptics are necessary in the presence of a satisfactory closed anastomosis. If the anastomosis is unsatisfactory, all the drugs in the pharmacopeia are probably inadequate to correct the situation.

The Poor-Risk Patient

It is in the poor-risk patient that the following four items demand careful consideration: water requirements, electrolyte needs, loss of blood and caloric and nitrogen requirements.

Water and electrolytes. It is convenient to consider together the problems hedging about the administration of fluid and electrolytes to patients before as well as after operation. So much has been written about the fluid and electrolyte needs of patients that it would be out of place for me to restate what others, who have devoted serious study to the matter, have said before. In a sense, it is unwise to consider separately the need of a patient for water and electrolytes; they go hand in hand. When vomiting is absent, the patient slakes his thirst by drinking enough fluid to keep him comfortable. When fluids are administered para-orally, the urine output and the specific gravity of the urine serve as fairly satisfactory guides in determining how much fluid to give. The objective of the surgeon is to keep the patient in fluid and electrolyte balance, sparing him the ill consequences of large contractions or increases in fluid volume. Each morning, when the surgeon and his house staff make ward rounds, the fluid and electrolyte requirements of all patients not hydrating themselves are determined. The weighing scale is a worth-while agency in detecting early departures from the normal status of hydration. The urine output for the pre-

ceding twenty-four hours (6 a.m. to 6 a.m.) is noted together with the specific-gravity determinations of the urine, made by the nurse on the ward on three or four separate specimens. A twenty-four hour output of 1000 to 1500 cc, with a specific gravity in the range of 1.015 to 1.020, is regarded as optimal. These considerations hold for the period before as well as after operation. A fluid intake of 2500 to 3000 cc ordinarily takes adequate care of the situation. There is rarely any need to give patients fluid in the form of saline solution on the day of operation. Glucose solutions (5 to 10 per cent) suffice. If an inlying duodenal tube is in place to which suction is being applied, allowance must be made for loss of fluid and electrolytes through such an agency. A good working rule is to estimate the loss of sodium chloride at 5 gm per liter of gastric aspiration. The hazard of continuing to give saline solution after an inlying duodenal tube has been removed is real. Immediately after operation, owing to the vasodilating effects of anesthesia on the skin capillaries, the loss of water through cutaneous vaporization may be large. The face sheet of the hospital record provides space for all the items to be listed by the nurse. A careful appraisal of these various factors by the surgeon and his house staff once a day ordinarily suffices to keep the situation in hand. In cases in which the urine output for the preceding twenty-four hours falls below 800 to 1000 cc and the patient's weight varies more than 2 per cent from the preoperative normal, one of the surgical house officers reviews the situation again later in the day to ascertain whether the fluids and electrolytes outlined for the day at morning rounds were satisfactory.

The weighing scale is an important agent in keeping the patient in fluid and electrolyte balance. All patients on my service undergoing major surgery are weighed frequently — on admission and each day before surgery to ascertain the normal weight. The objective of the surgeon after operation is to keep the patient within a fluctuation that does not exceed or fall below the preoperative normal weight by more than 1 or 2 per cent. Fluctuations in weight of more than 3 per cent from the preoperative normal value are few indeed. Yet, strangely enough, such incidents can happen, usually when weighing has been discontinued because believed unnecessary. Constant vigilance on the part of the surgeon and his staff is necessary to obviate this type of occurrence. Gains in weight as well as losses may be observed.

In the normal course of events, a patient will have an indwelling duodenal tube in place after gastric resection for approximately forty-eight hours and after a colic resection for about seventy-two hours. In the postoperative period, the plasma chloride may be determined once or not at all, the urine output and specific gravity and the weight of the patient sufficing to denote a satisfactory status.

portable scale. A few months ago, Mr. John A. Melan, of the Scientific Apparatus Shop in the University of Minnesota, built for me a portable, bedside scale that permits weighing of the patient (Fig. 1). An electrically driven motor ele-

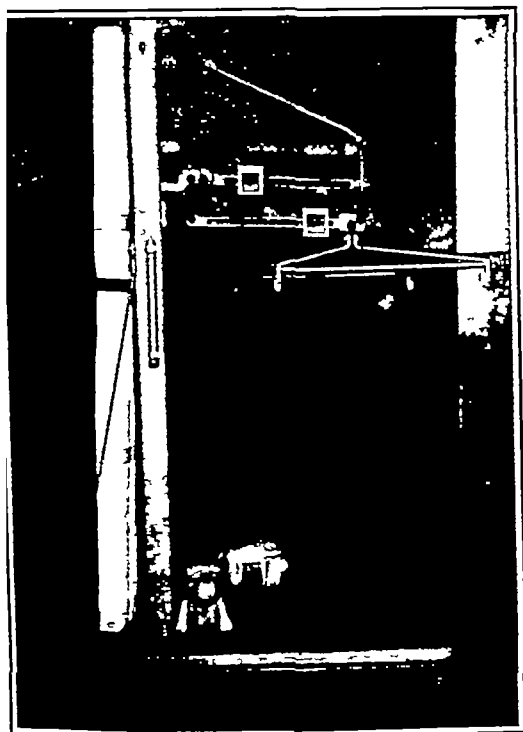


FIGURE 1 Scale Employed for Weighing the Patient in Bed

ates the patient in a hammock above the level of the bed (Fig. 2). This type of scale promises to prove helpful in dealing with sick patients. Weighing scales, like other apparatus, may go out of order and periodic checks for accuracy are imperative.

EXCHANGES BETWEEN THE INTRACELLULAR AND EXTRACELLULAR FLUID COMPARTMENTS

Hastings and Eichelberger¹⁶ observed that liberal amounts of normal saline solution injected intravenously into dogs caused a 48-gm gain per kilogram of muscle, detectable an hour after completion of the injection. In these experiments the dogs received 170 cc of saline solution (125 mg of sodium chloride and 25 mg of bicarbonate of soda) per kilogram. When, in addition, the hydrogen ion concentration was altered by the production of alkalosis employing a solution containing 114 mg of sodium chloride and 40 mg of bicarbonate of soda, the gain in weight per kilogram of muscle was 126 gm., of which amount the authors calculated the gain as 85 gm in extracellular fluid and 41 gm in intracellular. In other words, gains or losses in fluid sustained by the body are partitioned quickly,

in all likelihood according to a certain pattern, throughout the fluid-containing compartments of the body.

In studying dehydration Wiley and Wiley¹⁷ indicated that slight dehydration not exceeding 1.5 per cent of the body weight is probably unaccompanied by any great disturbance of the electrolyte balance. Inasmuch as 70 per cent of the body water is contained within tissue cells, it is apparent that ultimate fluctuations in the status of hydration of patients are due to contraction or swelling within them. Unfortunately, no direct means are available with which to measure changes in the intracellular fluid compartment, except so far as these changes are reflected in the extracellular fluids.

BLOOD LOSS

The employment of dry sponges that are weighed during operation permits the surgeon opportunity to inform himself concerning the extent of blood loss throughout the procedure. Only large packs in contact with the bowel are kept moist to keep fibrin formation at a minimum. The gain in weight of the sponges, passed back to be counted by the circulating room nurse, is calculated as blood loss, even though such gains in operations in the peritoneal and thoracic cavities are due in part to absorption of fluid other than blood. This scheme of calculating blood loss during operation has been in use in our operating rooms for somewhat more than four years.¹⁸ The plan has proved helpful, and a comparison with the usual colorimetric method for determining the blood loss suggests that this simple gravimetric method is quite accurate.¹⁹

In replacing fluid losses, there is no better rule than to replace in kind and in amount. In operations in which the anticipated blood loss is expected to exceed 500 cc, blood is always available for transfusion. In every major operative procedure, a needle should be placed in an ankle vein at the beginning of the operation, to permit the administration of glucose solution and blood or plasma if need be during operation. For blood losses in excess of 500 cc, there is no satisfactory substitute for the blood loss other than blood.

MAINTENANCE OF CALORIC AND NITROGEN EQUILIBRIUM

Within recent years, surgeons have become increasingly aware of the great importance of ascertaining the nutritional status of their patients prior to operation. It is not enough to make certain that the hemoglobin value is satisfactory and that the patient is in fluid and electrolyte balance. Patients whose food intake has been poor and who have lost considerable weight and, in consequence, have become autocannibalistic are poor subjects for operation. The protein stores of such patients have been depleted, and fatty infiltration of the liver is a usual sequel. The tolerance of such patients for

been employed as a matter of routine in computing fluid balance. Our experience suggests that the weighing scale is superior to other procedures in ascertaining early departures from the normal status of hydration in postoperative patients. In the weighing of patients the method can be carried out to an accuracy of about 100 gm. In a patient weighing 70 kg this figure represents 0.14 per cent of the body weight, in a patient weighing 50 kg, a margin of 100 gm in the accuracy of the method amounts to 0.20 per cent of the total weight. Since only changes ascribable to likely differences in the weight of body water are involved in attempting to follow the status of hydration with the weighing scale, employing the factor of 70 per cent of body weight as water, the accuracy indexes for patients weighing respectively 70 and 50 kg are 0.20 and 0.29 per cent.

For observations of an experimental nature, it is preferable to have a scale that weighs to an accuracy of approximately 5 gm. For clinical purposes, however, the ordinary weighing scale suffices. Over the short interval during the postoperative period, when the weighing scale is being employed to gauge the status of hydration, the error introduced, by assuming that observed changes in body weight represent differences in body hydration, is probably small indeed. The basal caloric requirements of the patient after operation are almost met by the daily intravenous administration of 3000 to 3500 cc of 10 per cent glucose solution. And the urinary nitrogen loss under these circumstances is ordinarily not large, especially when small amounts of plasma are given intravenously each day in an attempt to cover the protein demands of the body.

If the surgeon is relying principally on changes in the hemoglobin to afford the same orientation, it is obvious that this method is by no means so delicate as the weighing scales. A change of 1 gm in the hemoglobin from a previous determination of 13.5 gm suggests a 7.5 per cent alteration in hydration—a figure that is synonymous with severe dehydration or overhydration. Fluctuations of hemoglobin determinations in the normal patient in the range of 5 to 10 per cent are frequent enough in the experience of clinicians to suggest that adjudication of the status of hydration by changes in hemoglobin is not reliable, especially in detecting early or lesser variations in hydration. And it is just such early departures from the normal that the surgeon should be apprised of in following the status of hydration of his patient in an intelligent manner. It is fair to suggest that the weighing scale is probably twenty-five to fifty times more sensitive than the hemoglobin determination in the detection of minor changes in body hydration in postoperative patients.

In addition to the circumstance of greater accuracy over other available methods in determining the status of hydration, the weighing scale has the advantage of simplicity. Its chief virtue lies, however, in affording a prevision of what will happen

if abnormal losses or increases in body weight are not avoided.

Why have clinicians not adopted this device earlier to aid them in ascertaining the status of hydration of their patients? When will the weighing of cardiac patients become standard practice as a guide to therapy? In how many patients with urinary obstruction is the uremia observed after transurethral resection in reality extrarenal, owing to disorientation on the part of the surgeon in attempting to regulate fluid and electrolyte balance? Such patients as a group, because of their age and debility, are probably especially susceptible to errors in fluid therapy. Certainly, postoperative uremia is frequently observed among patients who were not uremic prior to operation. Is this circumstance inherent in the disease process, or is it a complication of therapy?

It is a frequent weakness to ask others to do what we might do better for ourselves. To this frailty, surgeons are no exception. We could weigh our patients, gaining thereby first-hand information relative to the status of hydration. But the laboratory will do this for us. We could examine the patient ourselves, but a note in the consultation basket to the medical staff will accomplish that objective more readily. We could make our own diagnoses, but why bother when we have roentgenologists and pathologists to make them for us? Have surgeons improved their technic by this sluggish indifference to some of their own important problems? When will they awaken from their torpid lethargy to a realization that they alone can significantly influence their own development? Other medical specialists are too occupied with their own problems to take a vital interest in ours. It is time that we grasp the necessity of helping ourselves out of some of our own difficulties. General recognition of the value of weighing patients will help the surgeon in his wrestle with the problem of hydration. Moreover, it is probably the best instructional agency in making a staff of both surgeons and nurses conscious of hydration. Of course, in many cases this extra labor is unnecessary. But who knows when this information will be at a premium? And who counts the cost of labor when lives are at stake? The time will certainly come when weighing patients will be as much a part of hospital procedure as taking the patient's temperature. Only time and patience, however, can overcome so powerful a force as the apathy of inertia.

Technic With the adoption of early ambulation of postoperative surgical patients as a frequent practice, most patients, on the day following operation, — even after major abdominal procedures, — are asked to stand on an ordinary portable scale brought to the bedside. Until recently, when patients returned from the operating room, they were lifted onto a Red Cross litter carrier, placed on an elevated block or platform on the same type of

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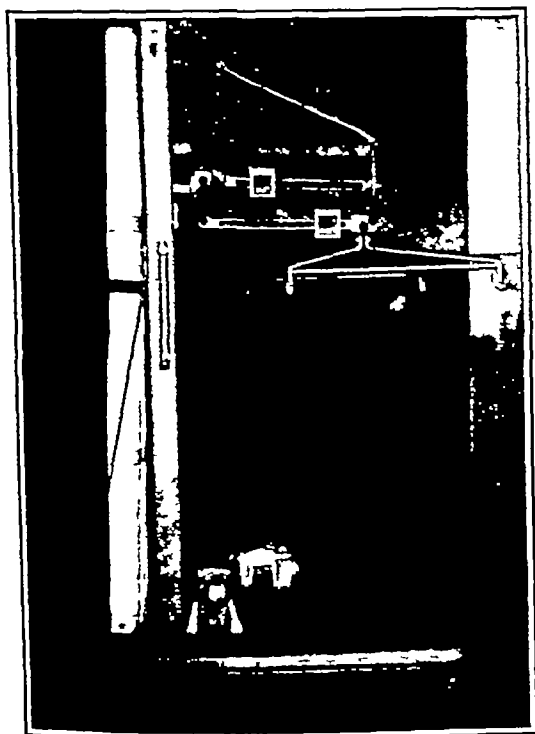


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if abnormal losses or increases in body weight are not avoided.

Why have clinicians not adopted this earlier to aid them in ascertaining the status of hydration of their patients? When will the weighing of cardiac patients become standard practice as a guide to therapy? In how many patients with urinary obstruction is the uremia observed after transurethral resection in reality extrarenal, owing to disorientation on the part of the surgeon attempting to regulate fluid and electrolyte balance? Such patients as a group, because of their age and debility, are probably especially susceptible to error in fluid therapy. Certainly, postoperative uremia is frequently observed among patients who were uremic prior to operation. Is this circumstance inherent in the disease process, or is it a complication of therapy?

It is a frequent weakness to ask others to do what we might do better for ourselves. To this frailty, surgeons are no exception. We could weigh our patients, gaining thereby first-hand information relative to the status of hydration. But the laboratory will do this for us. We could examine the patient ourselves, but a note in the consultation basket to the medical staff will accomplish that objective more readily. We could make our own diagnoses, but why bother when we have roentgenologists and pathologists to make them for us? Have surgeons improved their technic by this sluggish indifference to some of their own important problems? When will they awaken from their torpid lethargy to a realization that they alone can significantly influence their own development? Other medical specialists are too occupied with their own problems to take a vital interest in ours. It is time that we grasp the necessity of helping ourselves out of some of our own difficulties. General recognition of the value of weighing patients will help the surgeon in his wrestle with the problem of hydration. Moreover, it is probably the best instructional agency in making a staff of both surgeons and nurses conscious of hydration. Of course, in many cases this extra labor is unnecessary. But who knows when this information will be at a premium? And who counts the cost of labor when lives are at stake? The time will certainly come when weighing patients will be as much a part of hospital procedure as taking the patient's temperature. Only time and patience, however, can overcome so powerful a force as the apathy of inertia.

Technic With the adoption of early ambulation of postoperative surgical patients as a frequent practice, most patients, on the day following operation, — even after major abdominal procedures, — are asked to stand on an ordinary portable scale brought to the bedside. Until recently, when patients returned from the operating room, they were lifted onto a Red Cross litter carrier, placed on an elevated block or platform on the same type of

It is unwise to permit patients to struggle unduly during the waking period. I have the impression that patients with poor cardiac reserve often do not tolerate such struggling. I have seen at least one case—that of a patient with an antecedent coronary thrombosis—in which violent, uncontrolled struggling for a few minutes during the waking period was followed by sudden death. In any case, such violent exertion on the part of a semiconscious patient is productive of no good. When this circumstance arises, our nurses are instructed to give a small dose of Pentothal through the tubing leading to the ankle vein, into which the intravenous drip glucose solution begun at the commencement of the operation is still running. Such postponement of waking lessens the excitement of recovery from the effects of the anesthetic and affords the nurse time to cover the oncoming pain with a suitable dose of narcotic.

Regurgitation into the lungs is the most frequent cause of pneumonia whether such fluid comes from the stomach or is aspirated into the lungs from secretions in the mouth during the early phase of the recovery period.²² Keeping the stomach empty during and after operation by suction applied to an indwelling duodenal tube is therefore essential. Moreover, this practice is the best prophylaxis against intestinal distention, which frequently attends abdominal operation. The avoidance of distention and continued elevation of the legs above the level of the heart, together with active leg motion by the patient for the first few days during the recovery period are important items in the return of venous blood from the lower extremities and in preventing venous stasis and thus helping to thwart the formation of thrombi in the leg veins and their propagation as emboli.

Early ambulation of patients after operation quickens recovery and lessens the length of hospital stay. Recovery without complication is compounded of satisfactory preparation of the surgeon and the dissection and the care of the patient before and after operation. Simultaneous performance of multiple operations, such as gastric resection, cholecystectomy and appendectomy or gastric resection and partial colectomy, is well tolerated if nothing is left to chance in any part of the operative procedures. A smooth convalescence is synonymous with recovery and permits early dismissal from the hospital. It is not unusual for patients to leave the hospital five days after a gastric resection when the precepts of a well conducted operative procedure have been observed.

SUMMARY

The safe conduct of the patient through operation demands proper preparation of the surgeon, careful and precise preparation of the dissection and evaluation of the patient's condition for operation, including satisfactory preparation for the operative

procedure and watchful and intelligent care and observation through the convalescent period.

In the evaluation and maintenance of a proper fluid and electrolyte balance during the recovery period, the importance of the weighing scale is emphasized. It is believed that the routine weighing of patients undergoing major operative procedures that require the parenteral administration of fluid will materially reduce the incidence of errors in fluid therapy. In the early detection of deflection from the normal status of hydration, the weighing scale is probably twenty-five to fifty times more sensitive than changes in the hemoglobin in pre-empting the occurrence of threatening disaster to the patient occasioned by unwise administration of fluid and electrolytes. A method of weighing patients in bed after operation is described.

The success of operative procedures is a blend of many things, sovereign among which is a consecrated devotion to his tasks by the surgeon, together with a capacity for detection and critical analysis of the source and accountability of errors.

REFERENCES

1. Gamble J. L. and Ross S. G. Factors in dehydration following pyloric obstruction. *J Clin Investigation* 1:403-423, 1925.
2. Gamble J. L. and Melver M. A. Effects of pyloric obstruction in rabbits. *J Clin Investigation* 1:531-545, 1925.
3. Coller F. A., Bartlett, R. M., Bingham D. L. C., Maddock, W. G., and Pederson S. Replacement of sodium chloride in surgical patients. *Ann Surg* 108:769-782, 1938.
4. Coller F. A., and Maddock, W. G. Water and electrolyte balance. *Surg Gynec & Obs* 70:340-354, 1940.
5. Coller F. A., Campbell K. V., Vaughan H. H., Job V., and Moyer C. A. Postoperative salt intolerance. *Ann Surg* 119:533-542, 1944.
6. Gamble J. L. Extracellular fluid, extracellular fluid and its vicissitudes. *Bull Johns Hopkins Hosp* 61:151-173, 1937.
7. *Idem*. Extracellular fluid, renal defense of extracellular fluid, control of acid base excretion and factors of water expenditure. *Bull. Johns Hopkins Hosp* 61:174-197, 1937.
8. *Idem*. *Chemical Anatomy, Physiology and Pathology of Extracellular Fluid. A lecture syllabus*. Boston: Spaulding Moss, 1939.
9. Zintel H. A., Rhoads J. E., and Ravdin J. S. Use of intravenous ammonium chloride in treatment of alkalosis. *Surgery* 14:728-731, 1943.
10. Hartmann A. F. and Senn M. J. E. Studies in metabolism of sodium lactate. II. Response of human subjects with acidosis to intravenous injection of sodium lactate. *J Clin Investigation* 11:337-344, 1932.
11. Wilder T. S. and Drake T. G. H. Metabolism of chloride and total fixed base in pneumonia and relation to salt and water retention. *J Clin Investigation* 7:353-364, 1929.
12. McCance R. A. and Widdowson E. M. Secretion of urine in man during experimental salt deficiency. *J Physiol* 91:222-251, 1937.
13. Frank, H. A., Seligman, A. M., and Fine J. Treatment of uremia after acute renal failure by peritoneal irrigation. *J A M A* 130:703-705, 1946.
14. Jones C. M. and Eaton F. B. Postoperative nutritional edema. *Arch Surg* 27:159-177, 1933.
15. Wangensteen, O. H. Cause and prevention of stomal obstruction in gastrojejunostomies, gastric resection and gastrojejunostomy. *H. Braun Med-Surg Treatise* pp 551-562, 1942.
16. Hastings A. B., and Eichelberger L. Exchange of salt and water between muscle and blood. I. Effect of increase in total body water produced by intravenous injection of isotonic salt solutions. *J Biol Chem* 117:73-93, 1937.
17. Wiley F. H. and Wiley L. L. Inorganic salt balance during dehydration and recovery. *J Biol Chem* 101:83-92, 1933.
18. Wangensteen, O. H. Controlled administration of fluid to surgical patients including description of gravimetric methods of determining status of hydration and blood loss during operation. *Minnesota Med* 25:783-789, 1942.
19. Baronofsky I. D., Treloar A. E., and Wangensteen, O. H. Blood loss in operations: statistical comparison of losses as determined by gravimetric and colorimetric methods. *Surgery* 20:761-769, 1946.
20. Varco R. L. Preoperative dietary management for surgical patients with special reference to lesions of stomach and duodenum. *Surgery* 19:303-378, 1946.
21. Wangensteen, O. H. Abdominal surgery in old age, including comment on use of suture safety of multiple simultaneous operations: mechanism of development of "bed sores". *Journal-Lancet* 64:178-183, 1944.
22. *Idem*. *Intestinal Obstructions. A physiological and clinical consideration with emphasis on therapy, including description of operative procedures*. Second edition, 484 pp. Springfield, Illinois: Charles C. Thomas, 1942.

operation is poor. My associate, Dr R L Varco,²⁰ has made a special study of the preparation of such patients for operation, and the lessons learned in this clinic regarding adequate preoperative preparation may prove helpful to others. What the proper feeding of such starved and debilitated patients will accomplish is sometimes difficult to believe. A bed-ridden patient who can scarcely sit or stand may, with proper preoperative feeding, be rehabilitated to withstand severe operative ordeals. The extent of the weight loss is, in the main, the best criterion of the length of preoperative feeding period. Patients without pyloric obstruction may be fed with the intragastric drip of a feeding mixture rich in protein and carbohydrate and low in fat (the Varco II diet)

vitamin prior to operation. Vitamin K, in the preparation of patients with obstructive jaundice, has been a great boon in doing away with the hazard of postoperative bleeding in such cases. Poor-risk patients being prepared for major operative procedures, as well as in the early postoperative period, are given daily with the intravenous fluids an ampoule of crude liver extract (Campolon) and 100 mg of vitamin C. No attempt has been made to repair other likely coexisting vitamin deficiencies.

SPECIAL POSTOPERATIVE PROCEDURES

The employment of inhalation anesthesia has been standard practice in our clinic. The importance of the careful handling of an unconscious patient can

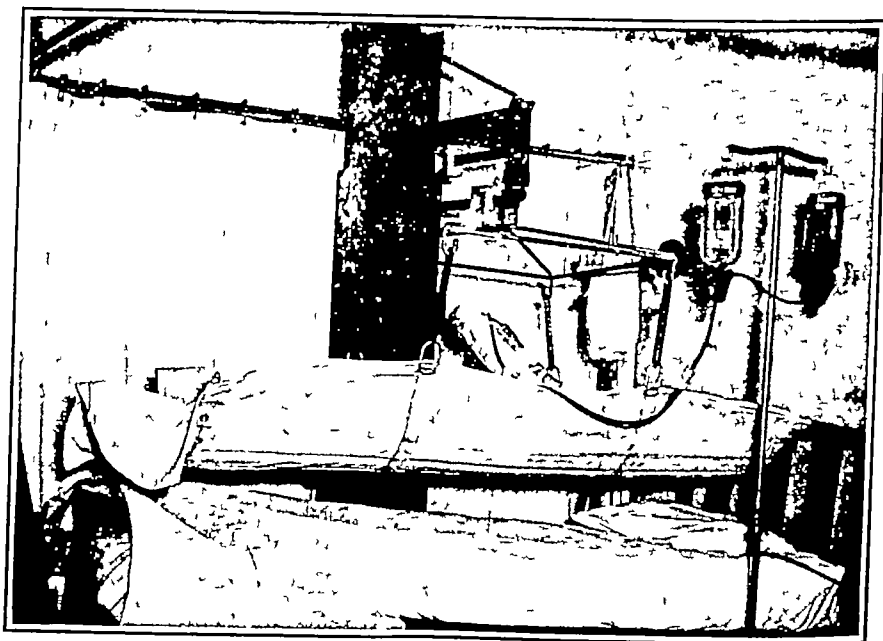


FIGURE 2 The Scale in Use

The motor on the platform (Fig. 1) has elevated the patient above the level of the bed. Neither the administration of intravenous fluid nor the suction applied to the indwelling duodenal tube is disturbed.

If a patient is able to eat, he may drink the mixture or take it through a sipper.²¹ For patients with pyloric obstruction, the preoperative preparation must be accomplished by the intravenous feedings of amino acids, plasma and glucose. Obviously, the oral route permits a more adequate and satisfactory preoperative preparation. Yet we have found preliminary enterostomy for feeding purposes unnecessary in the presence of pyloric obstruction, intravenous feeding sufficing to permit a one-stage operation.

VITAMINS

Studies on the poor healing quality of tissues in patients with vitamin C depletion suggest that all poor-risk patients be given adequate amounts of the

not be overemphasized. He should be conveyed from the operating room in moderate Trendelenburg position to encourage the gravitation of tracheal mucus or fluid into the pharynx, where it may readily be aspirated. Until the patient is wide awake and can deal satisfactorily with secretions that accumulate in the mouth, it is essential to provide for their removal. The use of a moderately steep Trendelenburg position during the waking period and an electric-suction device, operated by an experienced nurse oriented in the problems of the hazards of aspirated oral secretions, meets the needs of the situation. Intelligent bedside nursing care is a vital desideratum in the safe conduct of a patient through a major operative procedure.

ptic ulcer, 19 cases; carcinoma of lung, 16 cases, carcinoma of stomach, 16 cases, pulmonary tuberculosis, 15 cases, suppurative meningitis, 13 cases, cirrhosis of liver, 11 cases, carcinoma of prostate, 10 cases, carcinoma of bladder, 10 cases, and carcinoma of breast, 10 cases

About 50 per cent of the deaths occurred on the medical service, 35 per cent on the surgical and 15 per cent on the pediatric. The deaths were obstetric in only 1 per cent. Patient days in the hospital were distributed in about equal proportion

TABLE 1 *Data on Admissions, Deaths and Autopsies at Mary Hitchcock Memorial Hospital (1932-1944)*

DATUM	MALES	FEMALES	TOTALS	RATIO OF MALES TO FEMALES
Admissions	17,775	22,551	40,326	0.8
Deaths	812 (4.75%)	547 (2.63%)	1,359 (3.36%)	1.5
Autopsies	653	438	1,091	1.5

between medical and surgical cases, which together comprised about half the total. Pediatric cases accounted for 15 per cent and obstetric cases for 1 per cent of the total patient days.

A comparison of the age distribution of this group with that of all fatal cases in a large metropolitan region shows a correlation in some decades.² The percentage of deaths was highest in the first and lowest in the fifth decade in the group at the Mary Hitchcock Memorial Hospital, probably because the cases consisted solely of hospitalized patients. Infants born in the hospital contributed largely to the group of cases in which autopsy was performed in the first decade of life, accounting for nearly one tenth of the autopsies in this series.

The over-all importance of cancer as a fatal disease is indicated in this series, in which about one fifth of the deaths were due to cancer. If the cancerous diseases of the hemolymph system are grouped, they are second only to cancer of the large intestine in numerical importance.

Certain trends indicate that hospital death statistics cannot be compared with general death-certificate data. The development of special services

within a hospital is shortly reflected in the autopsy service. Changing therapies lead to increasing or decreasing hospitalization within a group. For the same reasons, comparison of data of different hospitals is difficult.

The numerical significance of such a series is so slight that the chief values of the service and analyses obviously accrue to the hospital and staff concerned. The purpose of this analysis and presentation is to emphasize the fact that, despite the lack of great contribution to general statistics, valuable information is afforded by routine autopsies to the small hospital and to medical groups that cannot be obtained in any other way.

This report includes only the data accumulated at the Mary Hitchcock Memorial Hospital. The consistently high percentage of examinations, however, is considered to be due in part to the program throughout the area. There has been co-operation of the small hospitals in the community, the Mary Hitchcock Memorial Hospital and the Dartmouth Medical School to achieve as high as 50 per cent of autopsies in individual small hospitals and in one physician's rural practice.³ During the period covered, autopsies have been done in and for ten participating institutions. Analysis of this series is in progress.

CONCLUSIONS

Autopsies should be a matter of routine. Only when the public is familiar with the value of autopsies will permissions be granted in a high percentage of cases.

Cases should not be selected for their "interest." Such selection defeats many of the purposes of the autopsy.

Autopsy statistics are of little value as statistics unless a high percentage of deaths are followed by autopsies that are routine.

Autopsies done in a high percentage of cases yield many valuable data not obtainable otherwise.

REFERENCES

1. House, R. K. Review of autopsy service in small rural hospital. *J. Tech. Methods and Bull. Internat. A. Med. Museums* No. 25 (December), 148, 1945.
2. Duffield, T. J. Vital statistics. City of New York Department of Health 1933-1935.
3. Putnam, W. F. Post-mortem examination in rural general practice. *New Eng. J. Med.* 224:324-328, 1941.

AUTOPSY SERVICE AT THE MARY HITCHCOCK MEMORIAL HOSPITAL*

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IN 1932 the Mary Hitchcock Memorial Hospital staff established standard autopsy procedures that have led to a consistently high percentage of permissions for post-mortem examination. The essential features of the program are as follows:

A hospital staff that agrees that all deaths be followed by a request for post-mortem examination. Precedence is given to the obtaining of permission for autopsy because of the fleeting nature of the opportunity to give a valuable service to the family of the deceased — I have never known a family to be antagonized by a request for autopsy.

A department of pathology ready to perform an autopsy at any hour of the day or night required by the circumstances. The effort required of the physician to obtain permission justifies an equal effort on the part of the pathologist to avoid delay and secure fresh material.

A public that is informed concerning the value of autopsy. Discussion of the facts of the case, particularly at the time immediately following autopsy, gives the pathologist an opportunity to answer many questions that, if left unanswered for long, may leave relatives in a puzzled frame of mind and cause them to seek the answers elsewhere. Following such an interview, the relatives are referred to the family physician, to whom a final complete report is sent.

A co-operative group of funeral directors. Frequent contact is required to determine possible improvements in technic or schedule and thus to avoid interfering with the funeral director's obligations to the family.

The continuity of the program is maintained by presenting to each new member of the staff the following statement:

An Approach to Securing Autopsy Permission

Autopsy percentage will be considered satisfactory when it reaches 100 per cent. Autopsies are done only after permission of the nearest relative or responsible person has been obtained, preferably by interview. It is important that relatives be aware of the following features of the autopsy service:

- 1 Autopsies are made without charge at considerable expense to give all concerned valuable information not otherwise obtainable.
- 2 Autopsies are done discreetly in such a manner as to avoid disfigurement of the body so far as the funeral is concerned. The method of autopsy makes better embalming possible for a competent embalmer.
- 3 Relatives should be assured that autopsy does not necessitate delay.

The purpose of the program was to approach as nearly as possible complete analysis of all hospital deaths. The results have been encouraging. Autopsies had been done in the region by medical school physicians for many years — the percentage during those years is not a matter of record, but was certainly low. Interest in autopsies, even without a formal program, resulted in an increase from less than 10 per cent (estimated) in 1926 to about 60 per cent after three years. The rise in the curve from this 60 per cent plateau followed the agreement of the staff members concerning the program and their complete co-operation in carrying it out.

In the twelve-year period 1932-1944, the Mary Hitchcock Memorial Hospital admitted a total of 40,326 patients. Figure 1 presents the autopsy

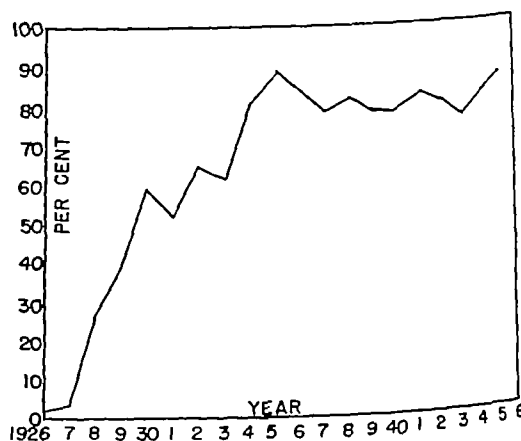


FIGURE 1. Curve of Percentages of Autopsies in Relation to Deaths (Mary Hitchcock Memorial Hospital, 1926-1945).

percentages. Table 1 indicates the sex distribution of patients admitted, patients dying in the hospital and patients autopsied. This distribution suggests that permission for autopsy is obtained with the same ease whether the patient is male or female. House¹ has analyzed and published elsewhere the data concerning most of these cases. The principal causes of death, exclusive of stillbirth, in 488 cases of the series of 1091 autopsies were as follows: hypertensive cardiovascular renal disease, 85 cases; coronary-artery sclerosis, 57 cases; rheumatic heart disease, 51 cases; carcinoma of large intestine, 46 cases; suppurative appendicitis, 32 cases; lobar pneumonia, 28 cases; pulmonary embolism, 25 cases; benign hypertrophy of prostate gland, 24 cases; subacute bacterial endocarditis, 20 cases;

*Presented at the annual meeting of the New Hampshire Medical Society, Manchester, May 14, 1946.

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In an earlier series of cases no systemic, toxic or allergic manifestations were observed²²⁻²⁴. More recently, however, we have noted local and generalized manifestations consisting of edema of the lips, the mucosa of the mouth and, in several cases, a generalized urticaria. The local reactions generally subsided after a change to another type of penicillin. In the urticaria in 1 case cleared up promptly when treatment ceased and did not return when a different type of penicillin was used. In a recent case with complicating urticaria we were able to continue with the same lot of penicillin by adding oral benadryl, this new synthetic antihistamine agent as apparently of value.

The apparatus used in our studies was the basic vaponefrin nebulizer* enlarged to a capacity of 2 liters to permit the utilization of the expired penicillin. This nebulizer produced a fine, voluminous mist or smoke screen with a particulate size of less than 1 micron. A piece of rubber tubing connected the nebulizer with a regulator attached to an oxygen tank. Oxygen flows of 5 to 7 liters were usually sufficient to aerosolize 10 cc of the penicillin solution in approximately fifteen minutes. To avoid loss of the drug in expiration, a glass Y tube was placed just proximal to the inlet of the nebulizer. The patient or nurse was instructed to close the open end with a finger during most of the inspiratory cycle and to remove the finger at the end of inspiration and during the entire expiration. With this technic the oxygen bypassed the nebulizer in the expiratory phase of respiration and no appreciable penicillin was lost through the top carburetor opening of the nebulizer. In the severest cases an automatic device perfected by Emerson delivered the penicillin aerosol during the inspiratory cycle by modifying a demand-type oxygen regulator. The lowering of pressure within the nebulizer at the start of inspiration released from the demand valve a flow of oxygen that then passed through the nebulizer. The penicillin aerosol in this technic was thus formed only on inspiration and did not require the co-operation of the patient. We recently modified our technic by attaching an Ohio humidifier directly to the regulator. The humidifier may be filled with hot tap water, which seems to add to the comfort of the patient. We are making further studies to determine whether it diminishes the occurrence of local reactions in the mouth and lips.

The nebulizer may be suspended or attached to a clivus stand for patients too sick to hold it themselves. We have found, however, that the majority of patients can comfortably hold the apparatus during the fifteen or twenty minutes of treatment. It is also advisable to have the nurse add 0.25 or 0.5 cc of physiologic saline solution at the end of the last daily treatment to clean out the nebulizer and to prevent further deposition of penicillin in the delicate horizontal and vertical rods of the apparatus.

*Obtainable from Vaponefrin Company, Upper Darby, Pennsylvania.

For patients who are unable to use the technic described above, the OEM mask can be employed. The nebulizer can be introduced into the face piece of the mask, and the oxygen entrance closed off. Infants and small children can best be treated in enclosed plastocene hoods or in specifically constructed closed chambers, the basic nebulizer and oxygen flows described above being used.

The basic Vaponefrin nebulizer can also be attached to the tracheotomy tube whenever topical penicillin aerosol therapy is desired in tracheotomy cases. We have found this of particular value in 2 patients with acute laryngotracheobronchial edema characterized by marked cyanosis and inspiratory retraction. These patients were moribund at the beginning of therapy. In these patients, instead of using oxygen, we have employed a mixture of 75 per cent helium and 25 per cent oxygen, introducing this mixture directly through the nebulizer. This technic may prove to be of lifesaving value in patients with laryngotracheobronchial obstructive disease.

Barach and his associates¹³ devised an apparatus for the introduction of penicillin aerosol into the nasal accessory sinuses following suction. We²⁵ employed this apparatus in a series of 24 patients with infective sinus disease and found it extremely efficient.

Prigal and Speer²⁶ recently described a method of aerosolizing penicillin by the use of steam in place of oxygen flows. This procedure may be of value in infants and children with infective croup, and the aerosol can be directed into the oxygen tent if humidification is particularly desirable.

PENICILLIN BLOOD LEVELS

Absorption of penicillin from the pulmonary tree into the blood stream was demonstrated by effective penicillin blood levels, which ranged from 0.015 to 0.225 units per cubic centimeter in one hundred and sixteen determinations (Fig 1). Large doses resulted in higher levels than did smaller doses, and the levels after crystalline† penicillin were higher than those after corresponding amounts of amorphous penicillin. Generally higher blood levels were obtained in patients with extensive lung involvement of a pyogenic type — that is, with pneumonia or lung abscess. Peak levels, which were observed at the end of thirty minutes, in some cases persisted for as long as two hours. The absorption of penicillin into the blood stream is not necessarily a measure of the topical effectiveness of penicillin aerosol. The blood levels vary according to the individual breathing pattern, equipment, dosage and type of penicillin, absorption variations of accumulated pus and secretions and the technic employed in the determination. In most of the cases the determination of blood levels is more of academic interest than of practical value. The clinical course is sufficient proof of the topical effectiveness of peni-

†Kindly supplied by Commercial Solvents Corporation, New York City.

PENICILLIN INHALATION THERAPY*

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BOSTON

INHALATION therapy has attained amazing prominence since the ancient and empirical practice of inhaling medicated vapors. In a report on the use of oxygen, helium and oxygen mixtures and aerosolized sprays of various therapeutic agents for the maintenance of respiratory function, the use of penicillin aerosol was suggested.¹ Barach and his associates^{2, 3} first described the technic and the value of continued vaporization of various drugs with oxygen streams. Castex et al,^{4, 5} Krueger et al,^{6, 7} and Mutch⁸ demonstrated that aerosolized substances penetrate to the outermost air sacs of the lungs and to the ends of the bronchial tree.

The physiologic rationale of penicillin aerosol therapy has been well established. Bryson et al⁹ demonstrated that penicillin aerosol penetrated the lungs, diffused into the blood stream and was excreted in the urine. Barach and his associates¹⁰⁻¹⁴ confirmed these observations in a group of patients with bronchopulmonary disease and developed the proper equipment and technic for penicillin aerosol therapy. In a detailed investigation of the fate of aerosols in the lungs, Mutch and Rewell¹⁵ further proved the efficacy of the therapy. They suggested the use of penicillin aerosol in the management of purulent bronchitis and bronchiectasis and as a prophylactic against secondary pyococcal infection in influenza. Knott and Clark¹⁶ carried these studies farther, demonstrating effective bacteriostasis in closed chambers and suggesting a technic for the control of airborne infections. Other investigators¹⁷⁻²¹ have employed penicillin aerosol with encouraging results in the management of pulmonary infections. In most cases effective therapeutic blood levels and excellent topical effects have been obtained.

This report concerns a summary of our findings in the use of penicillin aerosol in the treatment of 85 patients with bacterial pneumonia, suppurative bronchitis, bronchiectasis, lung abscess, infective bronchial asthma, infective laryngotracheobronchial edema, chronic pulmonary emphysema and emphysematous blebs.

TECHNIC

The control of infection by penicillin is dependent on the susceptibility of the bacteria, the resistance of the strain responsible for the infection, the dura-

tion of exposure of the organism to an effective local concentration of penicillin and the attainment of an adequate concentration of penicillin in the blood to penetrate the dense inflammatory foci in which the bacteria are embedded, the maintenance of such a constant high level is not essential in purely local pulmonary infections without bacteremia. Topical penicillin levels can be attained by the administration of concentrated doses six times daily. In patients with toxemia or septicemia additional intramuscular doses, five or six times daily, may help in producing blood levels sufficiently high to clear the blood stream of bacteria. Infections of the lung, which usually occur in well vascularized soft tissues, generally respond to concentrations of penicillin that are completely ineffective in the relatively avascular hard tissues.

The patients with pneumococcal pneumonia were treated for three to seven days, those with bronchiectasis or lung abscess, for seven days prior to surgery or for six weeks for purely medical therapy, those with infective bronchial asthma, from three days through three weeks, and those with streptococcal or staphylococcal pneumonia complicated by abscess formation, generally for a minimum of three or four weeks. The other patients were treated until there was no further evidence of infection and the penicillin-susceptible organisms had been eradicated.

The sodium or calcium salt of penicillin was used. Generally 25,000 units of penicillin were dissolved in 10 cc of physiologic saline solution and given at three-hour intervals for six to eight doses daily. The patients with pneumococcal pneumonia and those with acute or chronic sinusitis generally received 25,000 units at two-hour intervals for six doses and at three-hour intervals thereafter. The patients with the more serious types of pneumonia and lung abscesses received 50,000 units in 20 cc. of physiologic saline solution. These patients were able to take with complete tolerance 50,000 or even 100,000 units by the nasal route.

The calcium salt was less irritating but was usually more difficult to obtain than the sodium. The ampoules containing 200,000 units were of more practical value. Many patients objected to the taste and smell of the penicillin aerosol or found it irritating to the tongue or oropharynx. These complaints were minimized by a change to other lots of penicillin. A few patients developed sore tongues or stomatitis following the therapy. Saline rinses, dental hygiene and frequent sips of water during the treatment helped to diminish these complaints.

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 21, 1946.

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advisable to ensure complete eradication and to prevent exacerbations and abscess formations. To control pneumonia due to penicillin-susceptible strains of Friedländer's bacillus we have employed massive doses of 100,000 units at three-hour intervals in 2 cases. In one of these patients a blood level of 250 units of penicillin per cubic centimeter was obtained thirty minutes after the inhalation of 30,000 units. In both cases the organisms rapidly disappeared, remaining absent in one case during the course of therapy, in the other, however, the organisms recurred, although the patient remained symptom free for some time after the discontinuance of therapy. The patients with pneumococcal pneumonia required treatment for three to seven days. All were cured, with no ensuing complications, and they were generally discharged between the sixth and the eighth day after hospitalization. A brief abstract of a recently treated case of pneumonia follows.

A 28-year-old man entered the hospital with a complaint of pain in the right side of the chest of 4 days' duration. Two weeks prior to entry he had complained of a cough, productive of white frothy sputum. Examination revealed an acutely ill man. The temperature was 102°F. X-ray examination of the chest disclosed a typical pneumonia in the right upper lobe. Sputum culture revealed a Type 2 pneumococcus.

On admission a course of penicillin aerosol was started as follows: 50,000 units every 2 hours for six doses followed by 50,000 units every 3 hours until a total of 1,000,000 units had been given and, finally, 25,000 units every 3 hours, omitting the 3:00 a.m. dose daily. The temperature dropped to normal within 48 hours and remained essentially normal thereafter. A total of 2,115,000 units of penicillin was given over a 9-day period. Recovery was complete, and the clinical chart was similar to that in other cases previously reported.

INFECTIVE BRONCHIAL ASTHMA

A course of penicillin aerosol lasting from three days to three weeks was given to 22 patients with severe chronic infective bronchial asthma. The penicillin-susceptible organisms promptly disappeared and in most cases remained absent during hospitalization. This therapy was generally disappointing, although striking improvement was occasionally observed. In these patients control of the primary bronchial infection with intramuscular penicillin and oral sulfonamides has proved equally disappointing. Most of the patients observed, however, that they were able to raise sputum more easily while receiving penicillin aerosol. Many objected to the taste and the irritating qualities of the aerosol. The danger of local or generalized allergic reaction to penicillin aerosol in asthmatic patients must always be kept in mind. Most of the local and urticarial reactions observed occurred in patients with bronchial asthma or bronchiectasis.

A striking remission was observed in a patient with chronic intractable bronchial asthma who was treated in the Barach rebreathing hood apparatus with mixtures of 75 per cent helium and 25 per cent oxygen under positive pressure. In addition, penicillin aerosol was introduced directly into the hood

apparatus. Marked clinical improvement occurred after several days of such therapy. It was difficult, however, to evaluate the specificity of penicillin aerosol therapy in this case, for similar observations have been made in many patients treated with helium and oxygen under positive pressure without penicillin aerosol.^{23, 29}

BRONCHIECTASIS

A series of 30 patients with chronic bronchiectasis were treated with penicillin aerosol. Most of these patients received an initial course of therapy of at least six weeks and subsequently returned for an additional seven to ten days of therapy at intervals of three to six months. Postural drainage was carried out immediately before each treatment. Several of these patients continued to take penicillin aerosol therapy once daily at home throughout this period, this procedure was effective in preparing the patient for surgery and in preventing post-operative infections. Defervescence, lessening of toxicity, diminution in the amount of daily sputum, loss of its foul character, rapid disappearance of the penicillin-susceptible organisms, improvement in the patient's appetite and gain in weight were uniformly observed. Considerable improvement occurred in the bronchograms of several patients with involvement of a single lobe. This therapy was most helpful in the control and prevention of pneumonitis, which recurs in many patients with bronchiectasis. It was also of value in patients who were considered to be unsuitable for lobectomy or pneumonectomy or who refused to undergo such procedures. We are ever mindful that the anatomic changes accompanying bronchiectasis are permanent and cannot be altered by any type of therapy except resection. These patients are subject to repeated episodes of infection, pneumonitis or involvement of other lobes. The mucosal secretions in bronchiectasis largely result from the structural changes in the endothelial lining of the smaller bronchioles. Invasive organisms contribute by further destruction of the bronchioles. Infection can be eradicated or eliminated by penicillin aerosol, which thus provides the ideal therapy for preoperative and postoperative cases.

Many patients had previously received courses of intramuscular penicillin and oral sulfonamides without the striking effects obtained from penicillin aerosol, which effected longer periods of freedom from symptoms and recurrence of pneumonitis than other forms of therapy. The vital capacities of most of these patients increased from 30 to 40 per cent above the levels before aerosol therapy and remained fairly constant at the improved figure. Penicillin aerosol treatment can easily be carried out in the patient's home under supervision.

The penicillin-susceptible organisms uniformly disappeared from the sputum under such therapy. The appearance of gram-negative organisms, however, was observed in many patients who had been

cillin aerosol and is best demonstrated in patients with pneumonia

It was considered advisable to study the penicillin blood levels* in a series of 6 normal medical students receiving penicillin aerosol by the pulmonary route (Table 1) Inhalations of 50,000 units of sodium penicillin in 10 cc of physiologic saline solution were given with the technic described above Blood levels were obtained thirty minutes, one hour and two hours after the beginning of each treatment Similar studies were later performed on the same group,

peutic agent that could achieve greater topical efficacy and less systemic effect would prove of considerable value in combating chronic pulmonary disease

PNEUMONIA

Observations in this group of patients definitely proved the efficacy of penicillin aerosol in combating bacterial pneumonia and may serve as the rationale for its subsequent use in suppurative pulmonary disease Clinical cures were obtained in 9 patients with pneumococcal pneumonia and in 1 with an acute pulmonary infarct and pneumonitis The case histories and clinical charts of 6 of these patients were presented in an earlier report²¹ Blood levels of from 0.028 to 0.055 units per cubic centimeter were observed in 7 cases in which 25,000 units of penicillin had been administered Levels as high as 0.250 units per cubic centimeter were obtained when 50,000 units were employed in 2 other patients We

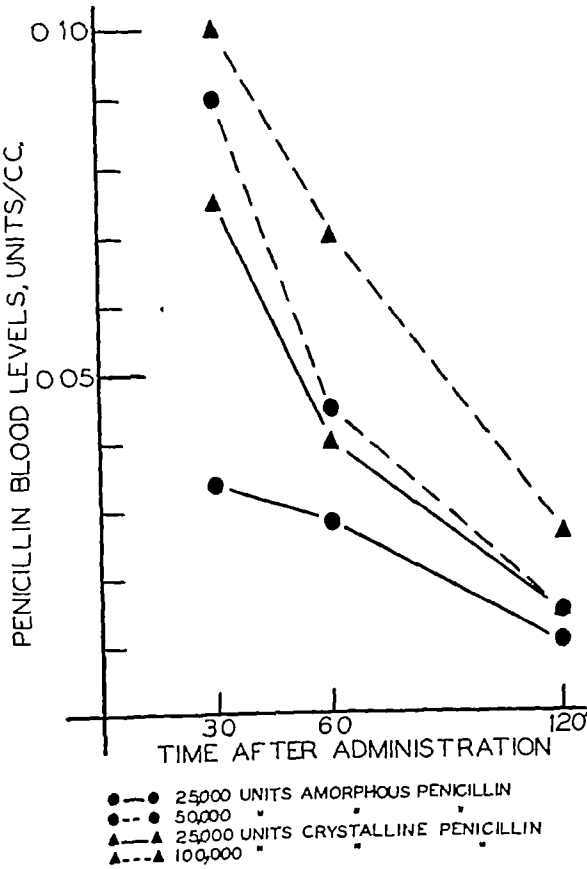


FIGURE 1 Average Penicillin Blood Levels following the Inhalation of Penicillin Aerosol

1.0 cc of 1 per cent Neosynephrine being substituted for the saline solution The average figures obtained with penicillin-Neosynephrine aerosol appeared lower than those obtained with penicillin-saline aerosol, particularly after thirty minutes and one hour This may be interpreted as indicating that Neosynephrine delays the absorption of penicillin through the pulmonary tree In vitro studies have demonstrated that penicillin fully retains its potency in solutions of Neosynephrine for as long as twenty-four hours²⁷ We are repeating these studies, employing 100,000 units in the same subjects, since a thera-

TABLE 1 Penicillin Blood Levels in Control Subjects following the Inhalation of 50,000 Units

SUBJECT	SOLVENT	PENICILLIN BLOOD LEVEL		
		30 MIN AFTER TREATMENT	1 HR. AFTER TREATMENT	2 HR. AFTER TREATMENT
		units/cc	units/cc	units/cc
1	Physiologic saline solution	0.078	0.039	0.019
	Neosynephrine	0.039	0.039	<0.019
2	Physiologic saline solution	0.078	0.039	<0.019
	Neosynephrine	0.078	<0.019	<0.019
3	Physiologic saline solution	0.078	0.078	0.039
	Neosynephrine	<0.019	0.019	<0.019
4	Physiologic saline solution	<0.019	<0.019	<0.019
	Neosynephrine	0.078	0.039	<0.019
5	Physiologic saline solution	<0.019	<0.019	<0.019
	Neosynephrine	0.039	0.019	0.019
6	Physiologic saline solution	0.039	0.039	<0.019
	Neosynephrine	0.039	0.039	0.019
Average	Physiologic saline solution	0.052	0.039	<0.019
	Neosynephrine	0.048	0.029	<0.019

do not advocate penicillin aerosol for the routine therapy of patients with pneumococcal pneumonia, the simpler procedures employing the sulfonamides or penicillin are preferable For the management of pneumonia due to streptococcal, staphylococcal and penicillin-susceptible strains of Friedländer's bacillus, penicillin aerosol therapy is probably more effective than parenteral therapy alone Combined aerosol and intramuscular therapy may be employed in patients who are seriously ill, particularly those with septicemia For patients with staphylococcal pneumonia the therapy should be continued for at least a week after all the clinical and roentgenographic signs of infection have subsided Since the lesions tend to become fibrosed and walled off, protracted therapy

*This work was aided by a grant from Frederick Stearns and Company

aerosol was then resumed for 10 days, at the end of which chest film revealed no evidence of the cavity and only light residua of the lipiodol. The patient was then discharged symptom free.

ACUTE LARYNGOTRACHEOBRONCHIAL EDEMA

Six patients with laryngotracheobronchial edema associated with serious infection were treated with penicillin aerosol, constant streams of oxygen or mixtures of 75 per cent helium and 25 per cent oxygen being employed. These patients were moribund at the outset of therapy. The conventional methods of employing sulfonamides, parenteral penicillin and oxygen therapy by catheter, mask and tent had been tried with little benefit. Dramatic improvement was observed as soon as the inhalation program was instituted. It was the opinion of many observers that the recovery of these patients could be directly attributed to the above therapy. A brief abstract of a recently treated case follows.

A 56-year-old man gave a history of aphagia and progressive inspiratory dyspnea of 14 hours' duration. He was found sitting up in bed struggling for breath, with marked inspiratory stridor and some prolonged expiratory wheezes through both lung fields. The temperature was 102°F. The lips were cyanotic, and the patient appeared critically ill. He had inhaled considerable dirt and dust while attempting to clean an attic. After several hours of exposure he began to cough, raising blood-streaked sputum, and noticed some shortness of breath. A few hours later he was found in a state of collapse. Oxygen and aminophyllin were administered, with little effect. Tracheotomy was being considered immediately before we first saw the patient. His wife stated that he had an extensive history of hay fever and seasonal bronchial asthma but had been free of asthma for several years and had complained of but minimal hay fever while undergoing hyposensitization injections. He had also shown marked positive reactions to molds and dust. An aural consultant had found extensive edema of the fauces and larynx.

Inhalation therapy, consisting of 75 per cent helium and 25 per cent oxygen through the O.E.M. positive-pressure mask, was instituted at once. At the same time 25,000 units of penicillin were introduced directly into the face piece with the Vaponefrin nebulizer. Treatments were given at 3-hour intervals. Inhalations of helium and oxygen mixtures with the mask set at 2.0 or 4.0 cm. of positive pressure were carried out for ½ hour out of each hour. Supplemental intramuscular aminophyllin was administered from time to time. Preceding each penicillin aerosol treatment, inhalation of 10 cc Vaponefrin was introduced directly into the face piece. Improvement was striking from the beginning of therapy. The faucial and laryngeal edema subsided slowly and cleared entirely within 3 days, the respiratory stridor disappeared after 12 hours, the attacks of bronchospasm and coughing being easily controlled with the Vaponefrin inhalations, and the temperature returned to normal after the 2nd day. There were no complications, and recovery was complete on the 6th day of treatment.

PULMONARY EMPHYSEMA AND EMPHYSEMATOUS BLEBS

Patients with chronic pulmonary emphysema generally present a history of cough, progressive dyspnea even at rest, weight loss and weakness. Many develop severe clubbing of the fingers and cyanosis, in a few cases severe emphysematous blebs are present. Bronchiectasis and evidence of bronchospasm may also be found in many cases. The patients are subject to recurrent bouts of respiratory infections, and their pulmonary reserve diminishes with each bout. The prognosis is generally poor

and progressive respiratory failure develops. The patient can be made more comfortable with the use of 50 per cent concentrations of oxygen, aminophyllin and aerosolized bronchodilator drugs. Supplemental elevation of the diaphragms by manual manipulation in expiration and the use of a proper abdominal belt may be of considerable value. Oral sulfonamides have proved of little benefit in the prevention of recurrent infection.

We have recently observed striking improvement in a series of 6 patients with severe pulmonary emphysema when penicillin aerosol was added to the program described above. In one of these patients diffuse emphysematous blebs and a minimal basal bronchiectasis complicated the picture. In another a giant acquired cyst occupied the entire upper lobe of the right lung. The remaining 4 patients had uncomplicated pulmonary emphysema secondary to recurrent bronchial infections. These patients were considerably improved after a course of penicillin aerosol therapy of from one to six weeks. They had been treated with oxygen and bronchodilator drugs first but had developed more progressive dyspnea, cyanosis and cough. After penicillin aerosol administration the vital capacities improved slightly, and this improvement was maintained at home while the therapy outlined above was being continued. These remissions have been striking, although probably temporary.

We believe that all patients with severe pulmonary emphysema who fail to improve with treatment employing the principles discussed above should receive a course of penicillin aerosol therapy. A typical case history follows.

A 72-year-old physician complained of progressive cough and dyspnea of 6 years' duration. During the previous year the cough had been productive of 120 or 150 cc of whitish, mucoid sputum daily. He had received two intensive courses of intramuscular penicillin and a course of oral sulfonamides without clinical improvement. Examination of the lungs revealed diminished breath sounds, coarse moist rales at the bases and marked hyper-resonance throughout. A chest plate revealed severe pulmonary emphysema, blebs and minimal basal bronchiectasis. The vital capacity was 1800 cc. The patient was advised to restrict his activities, to wear an abdominal belt and to take Adnefrin capsules and inhalations of Vaponefrin. On this program he improved remarkably and was soon able to resume most of his activities.

He continued these activities without many complaints for 10 months, when he acquired an upper respiratory infection and the earlier symptoms returned. The dyspnea soon became severe, and cyanosis appeared for the first time. The amount of sputum increased to about 300 cc. daily and cultures revealed many alpha-hemolytic streptococci and *Aerobacter aerogenes*. The cough was harsh and paroxysmal. During these paroxysms the cyanosis became marked, and the respiratory rate rose to 30 to 40. The patient was acutely ill on admission.

A program of inhalation therapy was instituted as follows: intermittent use of the oxygen tent and oxygen sprays of Vaponefrin at 3-hour intervals, followed by 25,000 units of penicillin aerosol for six daily doses. The clinical course was stormy during the first 2 days. Paroxysms of coughing and obstructive breathing frequently occurred and on several occasions death from suffocation appeared imminent. Gradually, the cough became less severe and productive of thinner mucoid material. The respirations and pulse fell progressively to the high normal ranges. The pathogenic organisms disappeared from the sputum. At the end of 8 days of treat-

refractive to penicillin aerosol. A recent report by Olsen¹⁸ favored the use of streptomycin aerosol in such patients. He employed doses of 500,000 units a day by nebulization and reported negligible urine and blood levels. The streptomycin-susceptible organisms were uniformly eradicated, and favorable results were obtained in most cases. Our experience with streptomycin aerosol has been limited to 2 patients with Friedländer organisms. In our first trial with this drug the streptomycin-susceptible organisms rapidly disappeared when 100,000 units at three-hour intervals were employed but returned after several days of therapy. We then found it necessary to increase the dose. After a while the organisms became more resistive and could not be eradicated despite tremendous doses. The possible appearance of streptomycin-resistive strains with aerosol should be taken into consideration before such treatment is initiated. Barach has also called my attention to one of his patients who developed involvement of the eighth nerve, with ataxia, following the use of parenteral streptomycin therapy. It appears from the literature that streptomycin may prove of value in selected cases of pulmonary infection due to Friedländer, influenza or tubercle bacilli and that combined intramuscular and aerosol therapy may be efficacious in such cases. The practical usefulness of the drug, however, may be limited by its toxicity, the development of resistive strains and its cost.

A group of patients with sinus involvement either preceding or associated with bronchiectasis required special attention.²⁵ A number of these patients were treated with penicillin aerosol by the nasal route, suction being employed before the positive-pressure aerosol. The suppurative sinus disease was adequately controlled in most of these cases. The combination of sinusitis and bronchiectasis was found most difficult to treat adequately. The percentage of recurrences of active sinusitis and bronchiectasis has been higher in this group than in patients with uncomplicated bronchiectasis. Proper drainage and pressure therapy are important adjuncts to penicillin aerosol therapy by the nasal route in the management of acute and chronic purulent sinus disease. We consider this approach most valuable in the management of sinus disease and are indebted to Barach and his associates¹³ for the development of the proper equipment.

A brief abstract of a recently treated case follows:

A 45-year-old woman entered the hospital complaining of a productive cough, fever and malaise of 1 month's duration. During the previous 7 years she had had frequent bouts of fever, chilliness, chest pain and a productive cough, lasting for several weeks at a time. Between attacks she had remained well. Three years previously a diagnosis of bronchiectasis of the lower lobe of the left lung had been made by a lipiodol bronchogram. During each of the recent bouts a course of sulfonamides had been given, with good results. After several days of such therapy the infectious process (pneumonitis) usually subsided rapidly and recovery was fairly complete in 1 to 3 weeks.

The present illness started as usual with a "head cold" and was characterized by fever, cough and malaise. During the usual course of sulfonamides the sputum increased in amount to about 150 cc daily. Cultures revealed hemolytic streptococci and staphylococci. Physical examination and x-ray films revealed an atelectasis of the left lower lobe with slight retraction of the heart to the left. A course of penicillin aerosol, 25,000 units every 3 hours for six days, was started. Improvement quickly followed. The cough and sputum subsided after the 5th day of treatment. The organisms were no longer found in the sputum. The patient was greatly improved and as well as usual after 10 days of treatment.

Because of the persisting atelectasis, bronchoscopy was performed on the 11th day. The bronchi were patent throughout, and no secretions were found in the left lower lobe. Lipiodol was instilled, and the bronchogram revealed a minimal subsegmental bronchiectasis of the left lower lobe and a portion of the lingula, the entire lower lobe was considerably smaller than usual. Penicillin aerosol was continued for 3 days after this procedure, and the patient was then discharged. The therapy continued at home for a full 6 weeks' course. She had remained symptom free 3 months* following discharge.

LUNG ABSCESS

We have employed penicillin aerosol therapy in a series of 11 patients with lung abscesses. Our observations have impressed us with its value in the aerobic, nonodoriferous, postpneumonic type of lung abscess, the results with the anaerobic, putrid, atelectatic types were disappointing. Doses of 50,000 units of penicillin given at three-hour intervals were usually adequate. Postural drainage was generally carried out prior to each treatment. In the more toxic and putrid cases we employed simultaneously 25,000 units of penicillin intramuscularly. Therapy was continued for at least four weeks. With an effective program of penicillin aerosol it is possible to avoid surgery in most of these cases. In most of our cases we did not employ intramuscular penicillin along with penicillin aerosol. Clinical and roentgenologic confirmation of cure was obtained in all cases, in several cure was further confirmed by lipiodol bronchograms. A brief abstract of a typical case follows:

A 37-year-old Negro entered the hospital complaining of high fever, shaking chills and hemoptysis. Two weeks before admission he had developed a nonproductive cough, chills, the fever and pleuritic pain in the left side of the chest. The cough became productive of rusty sputum, later turned bloody and finally became rusty again, with a foul odor. The patient collapsed on the 15th day of the illness and was admitted to the hospital. He filled a box with putrid sputum during the first 12 hours in the hospital. The sputum smear revealed gram-positive and gram-negative diplococci, spirilla and fusiform bacilli. An x-ray film of the chest disclosed a pulmonary abscess opposite the left hilus.

A course of penicillin aerosol was started as follows: 50,000 units every 2 hours for six doses and subsequently every 3 hours until a total of 1,000,000 units had been given, after which the dose was reduced to 25,000 units every 3 hours, omitting the 3:00 a.m. dose. Postural drainage was carried out preceding each treatment. The temperature dropped rapidly to normal. The sputum rapidly lost its foul odor and cultures subsequently revealed *Proteus vulgaris* and also *Klebsiella pneumoniae*. The patient was permitted up and about after the 4th week.

At the end of the 5th week of continuous therapy, a shortage of penicillin occurred, and inhalations of 1 cc. of 5 per cent sodium sulfathiazole at intervals of 3 hours were substituted for a 10-day period. A bronchogram revealed a small cavity, measuring 1.5 by 1.0 cm, presumably in the lingula. Penicillin

*Now 10 months following discharge the patient is still symptom free.

MEDICAL PROGRESS

ABDOMINAL SURGERY

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DURING the past year many articles have appeared on the management of battle wounds of the abdominal viscera. It is not possible to do this subject justice in a general review of abdominal surgery. Doubtless, this valuable experience with abdominal wounds will be collected in a separate report and will become an authoritative contribution. Suffice it to say that the selection of well trained, up-to-date surgeons, guided by consultants experienced in teaching and practice, played an important part in the remarkably fine results obtained.

EARLY AMBULATION

Early ambulation is discussed by Blodgett and Beattie.¹ These authors made a comparative study of 238 consecutive patients with abdominal operations treated by early rising and 443 similar patients who were kept in bed seven or more days after operation. In both groups complications were expected. They followed closely the principles of early ambulation set down by Leithauser and Bergo.² First, the patient is turned on the side of the operative wound, and the knees are flexed. He is then assisted to a sitting position on the side of the bed, and the shoes are put on. He is helped to stand on a footstool and encouraged to take deep breaths and to cough. He is walked for 8 to 10 feet and allowed to sit in a chair for ten minutes, after which he is walked back to bed. This process is repeated twice daily until the patient can arise and walk unaided. The early risers had less pain in their wounds, were able to care for themselves on about the fourth postoperative day and were ready for discharge from the hospital much earlier than the patients in the control group. There were fewer cases of wound disruption and fewer pulmonary complications with early ambulation, but there was a somewhat greater incidence of thrombosis in the leg veins.

It is essential to point out that early ambulation is often not well understood by the nursing personnel and by the house staff. Patients are lifted to a chair and allowed to sit too long, which, in fact, is conducive to stasis in the leg veins. The omission of the putting on of the shoes before walking is a serious matter, since the abnormal strain on the calf muscles may produce soreness that can be mis-

interpreted as early venous thrombosis. The added burden of carrying out these maneuvers correctly is compensated for by the early resumption of self-care. That modern preparation, anesthesia, wound closure and fluid replacement make early ambulation safe and sensible is accepted. The beneficial results obtained with shorter periods of postoperative recovery, less nursing care and probably fewer complications are well worth while.

HERNIA

Haber³ suggests the use of a long, silk, guide suture, placed in healthy bowel just above the questionable segment in strangulated hernia. The loop in doubt is returned to the peritoneal cavity, and oxygen administered by mask for fifteen minutes. By gentle traction on the guide suture, the bowel is brought back into the wound for inspection. In 4 cases reported, the decision of viability was determined by this method. Doubtless, the circulation will have a better chance for restoration in its normal environment than by the usual technic of warm physiologic saline compresses on the exteriorized segment.

Fisher⁴ reports 6 cases of interstitial hernia from McBurney appendectomy incisions that were diagnosed preoperatively as inguinal hernia. The herniation had taken place through the defect in the peritoneum of the wound, and the omentum had dissected along the muscle planes to the inguinal canal, presenting at the external ring.

In 1934 Wangenstein⁵ reported the use of a large flap of fascia lata, turned cephalad and left attached at the upper end, for the repair of large inguinal and femoral defects. In a recent contribution he⁶ reports the use of this technic in the repair of large abdominal-wall defects. In 3 cases of extensive carcinoma of the bowel and in 1 with a huge dermoid tumor in which large segments of the abdominal wall had been sacrificed, the use of these large pedicle grafts of fascia lata were used successfully. One of the defects measured 24 by 18 cm. In 3 patients with upper abdominal defects, one of which measured 26 by 21 cm., repair was achieved by swinging the lower rectus fascia upward.

THE SPLEEN

Dunphy⁷ has made a timely contribution on the technic of splenectomy. He gives Balfour⁸ credit for the method used. Instead of the tedious dissec-

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ment the patient was transferred to his home, where the therapy was continued. Approximately 3 weeks after admission to the hospital he was up and about, feeling comparatively well. The cough was hardly noticeable and productive of but 15 or 20 cc of sputum daily. The vital capacity was 2400 cc. This improvement was maintained for several months. We believe, however, that this recovery is probably temporary, in view of the serious underlying pulmonary disease.

DISCUSSION

Penicillin aerosol therapy is of definite value in the management of serious respiratory disease. It can be carried out best with the simple rebreathing technic described above. This may be modified, depending on the age of the patient and the nature of the illness. Helium and oxygen streams may be employed instead of oxygen for patients demonstrating obstructive respiratory disease. The penicillin aerosol may also be directed into tents, masks and tracheotomy openings. Other chemotherapeutic, antibiotic and chemical drugs may be substituted for penicillin if indicated. Finally, the penicillin aerosol may be directed nasally for the management of patients with acute and chronic purulent sinus disease.

Penicillin aerosol therapy should not be employed by the nasal or pulmonary route for the management of the common cold. This infection generally runs a self-limited course despite all so-called "useful therapy." One must always bear in mind the possibility of the appearance of penicillin-resistant strains in all cases of repeated or prolonged penicillin aerosol therapy.

This treatment should be reserved largely for patients with the following conditions: purulent sinusitis, bronchiectasis, lung abscess, infective bronchial asthma, infective bronchitis, pulmonary infections with the streptococcus, staphylococcus or penicillin-susceptible strains of Friedländer's bacillus and infections secondary to underlying primary disease of the lungs, such as pulmonary emphysema, lung cysts and infarcts. Every attempt should be made to identify the organisms from the nose, throat and sputum before therapy is begun.

SUMMARY

Observations in the management, with penicillin aerosol, of 85 carefully studied patients with bacterial pneumonia, infective bronchitis, infective bronchial asthma, lung abscess, bronchiectasis, infective laryngotracheobronchial edema, pulmonary emphysema and pulmonary blebs are presented. Many of the patients were helped considerably, and some dramatically.

Penicillin blood levels were determined at intervals of thirty minutes, one hour and two hours after treatment, and one hundred and sixteen such determinations were charted. Peak levels were observed at the end of thirty minutes and in some cases persisted for as long as two hours. Generally,

the higher peak levels were observed with the higher doses and occasionally in the patients with suppurative processes, such as pneumonia and lung abscess.

Streptomycin aerosol was also employed in 2 cases of bronchiectasis due to Friedländer organisms, but streptomycin-resistant strains rapidly appeared and could not be eradicated despite tremendous doses. This phenomenon was not observed in the penicillin-aerosol-treated cases. Penicillin may be safely combined with streptomycin aerosol when indicated. Further studies employing streptomycin aerosol, perhaps combined with intramuscular therapy, may prove of value in the management of selected cases of laryngeal and pulmonary tuberculosis.

REFERENCES

- 1 Segal, M. S. Inhalation therapy in treatment of serious respiratory disease. *New Eng J Med* 229:235-241, 1943. Inhalation therapy. *Ibid* 230:456-465 and 485-493, 1944.
- 2 Richards, D. W., Jr., Barach, A. L., and Cromwell, H. A. Use of vaporized bronchodilator solution in asthma and emphysema: continuous inhalation method for severe asthmatic states. *Am J M Sc* 199:225-232, 1940.
- 3 Barach, A. L. Physiologically directed therapy in pneumonia. *Am Int Med* 17:812-819, 1942.
- 4 Castex, M. R., Capdehourat, E. L., and Pedace, E. A. Inhalation de substances nebuli a cedos comprobacion experimental de su poder de penetracion a nivel del aparato respiratorio. *Arch. esp. de enferm d op resp y tuberc* 9:1, 1934.
- 5 Castex, M. R., Capdehourat, E. L., and Laverello, A. Nuevo tratamiento de las supuraciones broncopulmonares: accion curativa de un preparado sulfamidico nebulizado. *Rev Asoc med esp.* 55:85-89, 1941.
- 6 Krueger, A. P., et al. Prophylaxis and treatment of experimental influenza by inhalation of immune serum. *Federation Proc* 2:181, 1943.
- 7 *Idem*. Inhalatory route for prophylaxis and treatment of experimental influenza. I. Distribution of inhaled material. II. Immune serum in prophylaxis and treatment. *Am J M Sc* 207:40-60, 1944.
- 8 Mutch, N. Inhalation of chemotherapeutic substances. *Lancet* 2:775-780, 1944.
- 9 Bryson, V., Sansome, E., and Laskin, S. Aerosolization of penicillin solutions. *Science* 100:33-35, 1944.
- 10 Barach, A. L., Oppenheimer, E. T., and Forman, J. Inhalation of penicillin in broncho-pulmonary infection. *New Eng J Med* 181:10-11, 1945.
- 11 Barach, A. L., Silberstein, F. H., Oppenheimer, E. T., Hunter, T. H., and Soroka, M. Inhalation of penicillin aerosol in patients with bronchial asthma, chronic bronchitis, bronchiectasis and lung abscess: preliminary report. *Ann Int Med* 22:485-509, 1945.
- 12 Eckman, M., Rumsey, C. C., Jr., Barach, B., and Barach, A. L. Demand apparatus for automatic delivery of aerosols during inspiration. *J Lab & Clin Med* 30:608-610, 1945.
- 13 Barach, A. L., Garthwaite, B., Soroka, M., and Anderson, F. F. Apparatus for introduction of penicillin aerosol into nasal accessory sinuses with case report of patient with chronic sinusitis. *Am J Med* 24:97-103, 1946.
- 14 Barach, A. L. Apparatus for inhalation of penicillin aerosol. *Med Hosp* (in press).
- 15 Mutch, N., and Rewell, R. E. Penicillin by inhalation. *Lancet* 1:468, 1945.
- 16 Knott, F. A., and Clark, W. H. Absorption of aerosol penicillin via lungs. *Lancet* 1:468, 1945.
- 17 Olsen, A. M. Nebulized penicillin: preliminary report of its role in management of surgical bronchiectasis. *Proc Staff Meet., Mayo Clin.* 20:184-194, 1945.
- 18 *Idem*. Streptomycin in treatment of chronic bronchiectasis: preliminary report. *Proc Staff Meet., Mayo Clin.* 21:53, 1946.
- 19 Hagena, E. W., Karp, M., and Farmer, C. J. Inhalation method for penicillin therapy: preliminary report. *Arch. Otolaryng* 41:333-336, 1945.
- 20 Vermilyea, H. N. Aerosol penicillin in general practice. *J A M A* 129:250-257, 1945.
- 21 Hanks, R. J. Nebulized penicillin in treatment of respiratory infections. *Texas State J Med* 41:253, 1945.
- 22 Segal, M. S., and Ryder, C. M. Penicillin aerosol in management of lobar pneumonia, bronchiectasis, lung abscess and infective bronchial asthma. *Bull New Eng M Center* 7:279-286, 1945.
- 23 *Idem*. Penicillin aerosolization in treatment of serious respiratory infections: preliminary report. *New Eng J Med* 233:747-756, 1945.
- 24 Segal, M. S. Progress in inhalation therapy. *Mod Med* 14:63-79, 1946.
- 25 Miller, D., and Segal, M. S. Unpublished data.
- 26 Prigal, S. J., and Speer, F. D. New method of aerosolization of penicillin, sulfonamides and other medications for inhalation therapy: preliminary report. *Bull New York M Coll., Flower & Fifth St. Hosp.* 8:21-25, 1945.
- 27 Burbridge, E. L. Personal communication.
- 28 Segal, M. S. Inhalation therapy in treatment of serious respiratory disease. *New Eng J Med* 229:235-241, 1943.
- 29 *Idem*. Advances in inhalation therapy, with particular reference to cardiorespiratory disease. *New Eng J Med* 231:553-556, 1944.

act that it seems incredible that the authors found only 430 cases recorded in the literature. To be sure, the vast majority of the cases have no apparent clinical significance. Seventy per cent occur in the upper gastrointestinal tract. The duodenum, stomach and jejunum are involved in that order of frequency. The rests, however, are found in diverticula of the stomach, duodenum and jejunum and in Meckel's diverticulum and also in the mesentery of the intestines, omentum, splenic capsule, gall bladder and bile ducts. Of the cases of clinical significance, 10 were in the stomach, 7 in the duodenum, 3 in the biliary tract and 2 in a Meckel's diverticulum. The largest, which was in the transverse mesocolon, measured 10.0 by 4.5 by 1.5 cm and was cystic, containing stones. Symptoms are similar to that of ulcer with bleeding. Cancer occasionally occurs. Hypoglycemia from aberrant pancreas is reported. Barbosa et al recommend removal of the rests when found and estimate that they will be observed once in each five hundred operations of the upper abdomen. It seems likely that this is a conservative estimate.

Acute pancreatitis occurring in previously cholecystectomized patients is discussed by Vuori,¹⁸ who encountered 4 such patients whose cholecystectomy had been performed from one and a half to four years previously. Cholecystectomy during the acute attack of pancreatitis was performed on 4 patients, 2 of whom developed further attacks of pancreatitis. Of 23 patients treated conservatively, 7 had recurrent disease. Vuori considers cholecystectomy to have no great prophylactic value in the prevention of pancreatitis. It seems reasonably well established, however, that gall bladders containing stones should be removed after patients have recovered from acute pancreatitis.

Adams and Nishijima¹⁹ present a new method of treating pancreatic cysts. In 2 cases the cysts were anastomosed to a jejunal loop with an enterointerostomy. In 2 others a pancreatic fistula was implanted in the jejunum. Five patients responded well to the usual method of marsupialization and drainage. Anastomosis of these cysts to the intestinal tract may be the method of choice, particularly if one is careful to shunt the main intestinal stream through a bypass.

Sailer and Zininger²⁰ report a case of a large islet-cell tumor without hypoglycemia in a forty-year-old woman with symptoms of duodenal ulcer. She was known to have had a mass in the epigastrium for two or three years. Exploration revealed a healed duodenal ulcer and a large nodular tumor involving the body and tail of the pancreas. Resection was done, and microscopic studies revealed an islet tumor of the delta-cell type, with local blood-vessel invasion. The patient received postoperative radiation but died of mesenteric thrombosis three years and ten months later. Autopsy revealed recurrence of the tumor in the remaining

pancreatic tissue, liver, mesentery, bladder and uterus.

David and Campbell²¹ bring the data concerning subtotal pancreatectomy for hypoglycemia up to date. They have collected the reports of 36 patients so treated, with 23 cases of recovery from hypoglycemia. Three of these were their own patients. Alloxan was ineffective in controlling the symptoms in all cases in which it was used. The authors believe that the reaction of human beings to this drug is different from that of experimental animals. It appears that the results justify subtotal pancreatectomy when a careful search fails to reveal an islet-cell tumor.

Whipple²² in his discussion of David and Campbell's paper, calls attention to the need for thorough mobilization of the duodenum to rule out tumor in the head of the pancreas. He had found the lesion in this location in 6 of 33 patients operated on. In 9 patients subjected to subtotal resection of the pancreas for hypoglycemia, the results were not good, and in 3 who were re-explored, the islet-cell tumor was found in the remaining head of the pancreas. Whipple further states that in some of the other 6 cases, he probably had not done a sufficiently radical subtotal resection. He remarks that total pancreatectomy is at times feasible and compatible with life.

An excellent review of radical surgery for lesions of the pancreas, as well as a detailed account of his personal experiences, is presented by Whipple²³. He has performed the operation on 8 patients in two stages and on 21 patients in one stage. Earlier experiences with the two-stage approach with the increased difficulties from vascular adhesions at the second stage led him to advocate the one-stage procedure. He states that adequate preoperative administration of vitamin K makes this practicable. Attention is called to the value of the observation and special handling of anomalous extensions of the uncinate process around the superior mesenteric vessels. Whipple refers to Brunschwig's²⁴ monograph on pancreatic tumors as an important contribution to the subject.

Waugh and Clagett²⁵ report the experience of the Mayo Clinic in radical operation for cancer of the ampulla of Vater and the head of the pancreas. Thirty patients have been operated upon, 20 by these authors. They prefer a one-stage approach but believe that operation on some poor-risk patients should be done in two stages. The follow-up results were disappointing in carcinoma of the pancreatic head but encouraging in lesions of the ampulla. The operative mortality was 20 per cent.

Dennis and Varco²⁶ in a collective review, found 104 cases of radical operation for carcinoma of the pancreas reported up to the time their paper was submitted for publication and added 13 new cases of their own. The total experience in the University of Minnesota hospitals at that time was with 46

tion of the pedicle as the primary step in the procedure, the spleen is freed from its loose diaphragmatic and peritoneal attachments by gentle manipulation. It is then possible to deliver the organ into the wound and accurately to secure its vascular attachments easily and under vision from in front as well as behind. This shortens the time of operation, reduces the amount of blood loss and prevents accidental injuries to the tail of the pancreas and the fundus of the stomach. Although this method has long been used by many surgeons, it is probably not so well known as it should be.

Rives⁹ added to knowledge in this field by describing a technic for simple delivery of the spleen when it was densely adherent from old inflammation. He suggested that by incision of the peritoneum above these attachments, the adherent peritoneum and the spleen could then be brought forward in the same manner used in the normally attached structure.

Babson and Morgan¹⁰ have added to the literature the reports of 2 cases of spontaneous rupture of an apparently normal spleen. There have been reports of at least 8 additional cases since 1937. It is difficult to be sure that many of these patients had not received trauma, with probable rupture of the spleen, some time previously. The delayed or secondary hemorrhage in such cases, occurring days or even weeks after the original and often ignored injury, is well known.

Best and Schmid¹¹ cite 3 cases of rupture of malarial spleens unassociated with trauma, treated with early diagnosis and splenectomy with recovery. They call attention to the possible increase of this complication of malaria in veterans who served in the Pacific zones. Mild exertion, coughing, sneezing and straining at stool are frequent causative factors. If the condition is unrecognized and the patient is not operated on, the mortality is 100 per cent, the average reported death rate in such cases is 50 per cent.

Waugh¹² has collected 15 cases of peritoneal autotransplants of splenic tissue following rupture of the spleen—9 by foreign and 6 by American writers. He reports in detail the case of a patient of his own who had been treated by splenectomy five years previously following an automobile accident. During laparotomy for hysterectomy, splenic implants the size of a pinhead to a pea were found scattered widely throughout the peritoneal cavity, particularly over the small bowel and cecum. Two of the implants were removed for microscopic confirmation.

Harmer and Chalmers¹³ have collected 163 reported cases of splenic cysts. Hydatid cysts were twice as frequent as those of any other type. They distinguish between true and false cysts: the former are dermoid, epidermoid, hemangiomatous, lymphangiomatous and serous cysts, and the latter are large and single and at one of the splenic poles,

with normal tissue elsewhere. They report in detail the case of a cyst in a twenty-four-year-old woman who had known she had a tumor mass for ten years. The specimen weighed 13 pounds and was 60 cm. in circumference.

Lazarus and Marks¹⁴ give an excellent discussion of primary malignant tumors of the spleen, with a review of the literature. These tumors, which are rare, are divided into two groups—primary non-vascular sarcomas, arising from the endothelium of the splenic sinuses, and malignant angiosarcomas. They are highly malignant and metastasize rapidly to the liver and less often to the lungs, the regional lymph nodes and the pancreas. The diagnosis may be suspected in a rapidly growing tumor that produces persistent pain, tenderness and cachexia. Early splenectomy is recommended.

Curtis and Movitz¹⁵ have established the importance of accessory spleens. In 174 consecutive cases of splenectomy and in 4 of abdominal exploration, they found one hundred and thirty-one accessory spleens in 56 patients, an incidence of 32 per cent. The number of accessory spleens varied from one to ten—26 patients had only one, and these were more frequent in the younger age group. The accessory spleens were located in the hilar region, the splenic pedicle, the retroperitoneal region near the tail of the pancreas, the great omentum, the colic ligamentary attachments, the mesentery of the small and large intestine and in the left adnexa in women. In all the multiple locations, there was always one spleen in the hilar region. This is explained on the basis of the embryologic development of the spleen. Curtis and Movitz point out the difference in true accessory spleens from a splenulus or splenosis often found in the abdominal cavity following ruptured spleens with hemorrhage. These authors attribute the failures, which generally occur following splenectomy for congenital hemolytic icterus and primary thrombocytopenic purpura, to the accessory spleens left in situ. They further warn against the danger of implants if the spleen is fragmented during its removal for these conditions.

Pugh¹⁶ has made an excellent collective review of splenectomy, with a historical background of interest. He discusses the indications, mortality rates and technic of operation. He adds 15 case reports of his own, with 1 fatal case due to other injuries and not related to the removal of the spleen.

THE PANCREAS

Pancreatic heterotopia is discussed by Barbosa et al.¹⁷ They review the literature and report 41 authenticated surgical cases, of which 25 were of clinical significance. The term "heterotopia" is applied to pancreatic tissue outside its usual or habitual location and without anatomic relation of continuity or of vascularization of the pancreas itself. These embryonic rests are seen so frequently during operations on the upper gastrointestinal

ound In the other 3 chronic infection and stones, the presence of arteriosclerosis, were apparently responsible for the bleeding. It is properly suggested that the gall bladder should be considered a possible source of obscure anemia of gastrointestinal origin. In 1931 White and Jankelson³⁶ reported similar cases and discussed the differential diagnosis in hemorrhage of gall-bladder origin. It is possible that this phenomenon may be based on the associated duodenitis secondary to inflammation of the gall bladder.

Norgore³⁷ collected from the literature 31 cases of traumatic rupture of the gall bladder, to which he added a case of his own in which the patient was a thirty-seven-year-old man who had been injured in an automobile accident. Attention was paid to a fractured left fibula until a few hours later, when the patient complained of abdominal pain. Seven days and a half hours after the accident, exploration revealed biliary peritonitis from a rent in the gall-bladder wall. The opening was closed, and cholecystostomy was performed, with uneventful recovery of the patient.

Extreme dilatation of the common hepatic ducts, with repeated operations for stones, sand and mud, are discussed by Sanders,³⁸ who has handled the problem in 22 cases by a generous lateral anastomosis between the enlarged duct and the duodenum, with satisfactory results. Usually, a wide dilation of the outlet of the duct, either by sharp incision or stretching, relieves this situation. Plastic operations from within the duodenum for this type of chronic dilatation with distal stenosis are described by Bailey.³⁹

Experience with benign stricture of the common bile duct at the Mayo Clinic is reported by Flickinger et al.⁴⁰ There were 188 patients, with a history of surgical trauma in 73 per cent. Symptoms were present immediately after cholecystectomy in 58 per cent, and there was a recognized accident during operation in only 9 per cent. Eighteen patients developed symptoms of hepatic-duct stricture three to twelve years after operation. It is significant that 12 per cent of all patients had been subjected to cholecystectomy in the absence of gallstones. All but 2 had had previous biliary-tract surgery. The usual procedure was choledochoduodenostomy or hepaticoduodenostomy. There was a 12 per cent operative mortality, 18 per cent of patients dying after leaving the hospital, 31 per cent continued to have symptoms. The 188 patients had had a total of two hundred and seventy-eight operations before admission to the clinic, and in these cases a total of two hundred and eighteen reconstructive procedures were done. Thirty patients who continued to have symptoms after re-establishment of continuity were finally well, 36 per cent of all survivors were well at the last report.

This distressing complication of biliary-tract surgery was discussed by Pearse,^{41,42} who made a collective review from correspondence with other

surgeons and from his own experience on the use of vitallium tubes in reconstructive operations for benign strictures of the bile ducts. Approximately 80 per cent of the patients had a satisfactory result at the time of his report. This is a high figure, and many of these patients will subsequently need further surgery to relieve the recurring symptoms. The discussion of the prophylactic measures concerning this problem is excellent. In only 1 patient out of 14 on whom the vitallium-tube method was used at the Massachusetts General Hospital was the final result apparently satisfactory. The duct in this patient had successfully been repaired over a vitallium tube used in the reconstruction two and a half years previously. When jaundice, pain, fever and chills brought the patient back to the hospital, the encrusted vitallium tube was acting as a large stone obstructing the outlet. Three other patients developed a new stricture — 2 above and 1 below the tube. The problem is serious, and repeated operations are often necessary before conditions are found that lend themselves to a suitable solution.

Peterson⁴³ has reported 42 cases of so-called "re-formed gall bladder," most of which resulted from a remnant of the gall bladder at the ampulla. Some apparently developed from a long cystic duct. Peterson considers the term a misnomer and believes that the condition actually represents the results of an incomplete operation. Symptoms are comparable to those in patients whose gall bladders have not been removed. In many cases the common bile duct is not dilated, as normally takes place following cholecystectomy, and symptoms are due to the intact nerve mechanism, which produces repeated spasm of the sphincter of Oddi. Peterson discusses the great care needed in cholecystectomy, with the absolute identification of all structures. It is pertinent to state that an incomplete operation under certain conditions of acute inflammation with edema about the ducts is preferable to the serious sequelae that often follow cholecystectomy.

Guyton⁴⁴ gives a case report of double gall bladder in a forty-two-year-old woman. Both bladders contained stones and were joined by a single cystic duct.

McLaughlin⁴⁵ operated on a twenty-five-year-old Negro who had suffered a weight loss of 25 pounds because of discomfort and a feeling of fullness after eating. A large tumor was palpated in the right upper quadrant, and a nonfunctioning gall bladder was reported after study. A large cyst of the choledochus was aspirated of 1000 cc of bile. This was dissected free from below upward, and all but a proximal remnant was removed. The remaining segment was anastomosed to the duodenum, with a good result.

Shallow et al.⁴⁶ collected from the literature 182 cases of congenital cystic dilatations of the common bile duct and reported 2 cases of their own. In the first patient, who was operated on in 1941,

cases of pancreatic cancer. Local excisions have been done in 9 cases, and radical operations in 14. In simple exploration the mortality was 23 per cent, and in radical extirpation, it was 29 per cent, whereas in local excision, it was 11 per cent. The authors consider most of the deaths to have been due to errors that are now avoidable. Like all surgeons experienced in this field, they prefer the one-stage operation, biliary-tract continuity from the common hepatic duct to the jejunum being established with implantation of the pancreatic duct. They believe that the gastrojejunostomy is best done about 40 cm distal to the implantation of these structures. This is a matter of choice, and most surgeons regard a much higher anastomosis between the stomach segment and the jejunum as satisfactory.

THE BILIARY SYSTEM

Clagett and Hawkins,²⁷ in an interesting case report, described the successful removal of the left lobe of the liver for multilocular cyst. A Bethune pneumonectomy tourniquet was used to control the base of the lobe during extirpation. Von Harbner is cited as having used a similar technic for the removal of a nonparasitic cyst in 1908. Such cysts in the liver are frequently associated with cystic disease of the kidneys. It is likely that many surgeons have had the opportunity to do this operation once or twice, but few reports have appeared in the literature.

Flynn²⁸ presents a timely discussion of the modern management of pyogenic liver abscess, with the successful treatment of 1 patient. He attributes his success to early diagnosis followed by adequate drainage and the use of penicillin. In the pre-chemotherapy era, the mortality for pyogenic liver abscess ranged from 50 to 95 per cent. In a recent case of an extremely large liver abscess of this type treated at the Massachusetts General Hospital, streptomycin was used following adequate drainage, with spectacularly quick sterilization of the abscess cavity.

Gatch, Battersby and Wakim²⁹ presented experimental evidence that cholecystitis is initiated by chemical action and that infection is due to the secondary invasion of bacteria on the chemically damaged gall-bladder wall. They produced acute inflammation in the gall bladders of dogs by introducing bile salts under pressure. Activated pancreatic juice caused acute edema and inflammation in the bile ducts of the animals when injected through the papilla of Vater. Stones in the gall bladder, with acute obstruction of the cystic duct, are believed to allow the imprisoned bile salts to damage the gall-bladder wall. Infection that follows depends on the degree of chemical action due to the duration of obstruction. Their deductions are as follows: early operation in acute cholecystitis is necessary only in fulminating cases, the gall bladder as a rule is not a focus of infection, prolonged

drainage is not necessary, there is little danger from spreading infection if the acute gall bladder is opened during operation, and exploration of the common hepatic duct is dangerous in the presence of acute edema and should be reserved for a later procedure if it becomes necessary.

Glenn and Heuer³⁰ present the results obtained in the New York Hospital in the treatment of acute cholecystitis over a thirteen-year period. They advocate early operation, which they have performed on 527 patients. Of 175 patients over fifty years of age, 9 succumbed, whereas only 4 of 352 under the age of fifty died. The over-all mortality was 2.5 per cent. Cholecystectomy was performed in 460 cases, being combined with choledochostomy in 43. Of the 67 patients treated by cholecystostomy alone, 5 succumbed. These results are in close accord with those at the Massachusetts General Hospital. The older the patient, the greater the risk, and in our series drainage of the gall bladder also carried a higher mortality rate than cholecystectomy.³¹

Johnstone and Ostendorph³² found 32 cases of perforation of the gall bladder in 12,000 consecutive cases at routine autopsy. One in every 375 persons in the group died of this complication. There were 22 men and 10 women in the series. General peritonitis was found in 42 per cent of cases, 47 per cent of the cases of perforation were undiagnosed before autopsy. The authors reported a series of 105 cases of acute gall-bladder disease treated surgically in which, as would be expected, the mortality was lower in patients operated on in the early days of the process.

Hicken and Coray³³ found spontaneous fistulas in some portion of the gastrointestinal tract in 42 per cent of their patients with biliary-tract disease. The fistulas were most frequently due to stone erosion, peptic ulcer and malignant disease ranking second and third as causes. Cholangiographic studies on the operating table are considered of great value in determining the extent and source of the fistula. Hicken and Coray advocate preventive measures by earlier treatment of gallstones and ulcer. Stage procedures are recommended, since the re-establishment of normal continuity of bile flow into the gastrointestinal tract leads to spontaneous closure of the fistula.

Goldman et al.³⁴ relieved 2 patients of residual common-duct stones with the introduction of Suby and Albright's solution G by means of Murphy drip through a T tube. They found, however, that this solution did not dissolve gallstones in a test tube. Since solution G is somewhat similar in composition to U.S.P. magnesium citrate solution, they concluded that the beneficial results were probably due to the relaxation of the muscle fibers of the papillary region by this drug.

Hudson and Johnson³⁵ report 4 cases of gastrointestinal hemorrhage from the gall bladder. In 1 a hemangioendothelial sarcoma of the gall bladder was

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 33041

PRESENTATION OF CASE

A sixty-nine-year-old married farmer was admitted to the hospital because of a gradually developing stiffness and pain of the right knee.

The patient stated that in childhood he had received a severe laceration of the anteromedial aspect of the right knee causing immobilization for about two months. Seven years before entry he noted the gradual onset of pain and stiffness of the knee, as well as the appearance of a mass on the inner aspect. The stiffness and pain had grown worse, and the mass had gradually increased in size until two years before admission, when the increase had become more rapid. A cast was applied, baking, massage and manipulations of the neck and knee were without benefit. During the year before entry the pain became severe and constant and the mass grew larger, the patient continued to work, however.

Physical examination revealed a hard, fixed, tender mass on the posteromedial aspect of the right knee over the medial side of the joint and the condyle, extending posterolaterally in the popliteal space and proximally along the medial portion of the hamstring muscles. The mass was about the size and roughly the shape of two lemons, but with indefinite edges. The skin was freely movable over the tumor mass. The knee was in 120° flexion, with slight motion either active or passive. The leg was in adduction on the thigh. The right inguinal region was tender to deep palpation, but no large definite lymph nodes were felt.

The blood pressure was 184 systolic, 100 diastolic. The routine laboratory data were normal. An x-ray film revealed slight decalcification of the bones of the right knee joint, which was otherwise normal. Posterior to the joint there was a soft-tissue mass, measuring 6.5 by 5 cm., that contained flecks of calcification (Fig. 1). The blood serum calcium was 9.2 mg., and the phosphorus 2.4 mg. per 100 cc., the phosphatase was 5.6 Bodansky units.

An operation was performed on the thirteenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. MERRILL C. SOSMAN* The x-ray films show a poorly defined mass that is best seen in the lateral view of the knee, on the film with the lighter exposure. The mass is made up of individual lobules, in some of which fine flecks of calcium are deposited. The mass extends beyond the upper end of the tibia and well up behind the femur, but there is no bone destruction. The joint looks quite normal in contour and width, and the mass is distinctly outlined in some sections, so that invasion of the soft tissues is not suggested. One of the first considerations with a mass anywhere in the body is to obtain a film of the chest. In the films in this case the lungs are clear of metastases. This looks discouragingly easy because the majority of firm nodular masses behind the knee, particularly if they contain small flecks of calcium, turn out to be synovial tumors. All of us, I am afraid, make the mistake of calling them "synoviomias." Do you call them "synoviomias" when you run across them?

DR. TRACY B. MALLORY We use that term because it is a standard one. I have never been altogether convinced that it was correct, however.

DR. SOSMAN Synovia, as I understand it, is the fluid in the knee joint. The synovial tissue, not the fluid, is the point of origin of the tumor, so that it is more accurately called "synovialoma." This was brought out by Jönsson† in an article based on 90 cases of malignant tumors of skeletal muscle, fascia, joint capsules and tendon sheaths, all of which had the same characteristics, irrespective of their point of origin. Histologically the tumors can be divided into the following eight groups: fibromyxosarcoma, endothelioma, spindle-cell sarcoma, hemangioblastoma malignum, angio-blastic sarcoma, what Jönsson called "polymorphous-cell sarcoma" (which is new to me but was so called, I suppose, because it had so many kinds of cells), alveolar sarcoma and round-cell sarcoma. These tumors, however, might be classified under a group of synovialomas of the malignant type.

Since the x-ray films suggest a synovialoma, I fear a trap, that diagnosis seems too simple. Of the other tumors that occur in this situation, a Baker cyst is one of the most frequent. Do you agree to that, Dr. Barr?

DR. JOSEPH S. BARR I think that it is the most frequent tumor in the popliteal space.

DR. SOSMAN The few I have seen were not so hard as this one was said to be, and none of them contained calcification. Have you seen calcification in a Baker cyst?

DR. BARR No.

DR. SOSMAN I therefore think that we can rule out a Baker cyst. The angiomas are usually softer.

*Roentgenologist, Peter Bent Brigham Hospital.

†Jönsson, G. Malignant tumors of skeletal muscles, fasciae, joint capsules, tendon sheaths and bursae. *Acta Radiol.* 20:105-127, 1939.

excision of the dilated common duct was performed, with anastomosis of the two hepatic ducts separately into the duodenum. The second patient had an enormous abdominal tumor, from which 5800 cc of dark-brown material containing bile and amylase was aspirated, an anastomosis was made between the cyst and the duodenum. Both patients were well and symptom free at the time of the report.

(To be concluded)

REFERENCES

1. Blodgett, J. B., and Beattie, E. J. Early postoperative rising. *Surg., Gynec & Obst.* 82:485-489, 1946.
2. Leithauser, D. J., and Bergo, H. L. Early rising and ambulatory activity after operation: means of preventing complications. *Arch Surg.* 42:1086-1093, 1941.
3. Haber, J. J. Use of guide suture in strangulated hernia. *Am J Surg.* 71:392-395, 1946.
4. Fisher, H. C. Postappendectomy interstitial inguinal hernia. *Ann Surg.* 123:419-426, 1946.
5. Wangenstein, O. H. Repair of recurrent and difficult hernias and other large defects of abdominal wall employing iliofemoral tract of fascia lata as pedicled flap. *Surg., Gynec & Obst.* 59:766-780, 1934.
6. *Idem*. Repair of large abdominal defects by pedicled fascial flaps. *Surg., Gynec & Obst.* 82:144-150, 1946.
7. Dunphy, J. E. Splenectomy for trauma: practical points in surgical technique. *Am J Surg.* 71:450-460, 1946.
8. Balfour, D. C. Technique of splenectomy. *Surg., Gynec & Obst.* 23:1-6, 1916.
9. Rives, J. D. Splenectomy: method of mobilizing spleen in presence of dense adhesions. *Surgery* 11:223-228, 1942.
10. Babson, W. W., and Morgan, P. Spontaneous rupture of apparently normal spleen. *Am J Surg.* 72:97-102, 1946.
11. Beat, R. R., and Schmid, J. F. Ruptures of malarial spleens unassociated with external trauma. *Surg., Gynec & Obst.* 82:731-734, 1946.
12. Waugh, R. L. Multiple peritoneal autotransplantation of splenic tissue following traumatic rupture of spleen. *New Eng J Med.* 234:621-625, 1946.
13. Harmer, M., and Chalmers, J. A. Splenic cysts: with report of case. *Brit M J* 1:521-523, 1946.
14. Lazarus, J. A., and Marks, M. S. Primary malignant tumors of spleen with special reference to endotheliomas. *Am J Surg.* 71:479-490, 1946.
15. Curtis, G. M., and Movitz, D. Surgical significance of accessory spleen. *Ann Surg.* 123:276-289, 1946.
16. Pugh, H. L. Splenectomy, with special reference to its historical background. *Internat Abstr Surg.* 83:209-224, 1946.
17. Barbosa, J. J., de Castro, Dockerty, M. B., and Waugh, J. M. Pancreatic heterotopia: review of literature and report of 41 authenticated surgical cases of which 25 were clinically significant. *Surg., Gynec & Obst.* 82:527-542, 1946.
18. Vuori, E. E. Vier Fälle von akuter Pankreatitis bei vorheriger Cystektomie. Einiges über Rezidive in einem Material von 46 akuten Pankreatisfällen. *Acta chir Scandinav.* 83:120-125, 1943.
19. Adams, R., and Nishijima, R. A. Surgical treatment of pancreatic cysts. *Surg., Gynec & Obst.* 83:181-187, 1946.
20. Sailer, S., and Zinninger, M. M. Massive islet cell tumor of pancreas without hypoglycemia. *Surg., Gynec & Obst.* 82:301-305, 1946.
21. David, V. C., and Campbell, L. K. Experiences in subtotal resection of pancreas in hypoglycemia. *Ann Surg.* 123:836-846, 1946.
22. Whipple, A. O. Discussion of David and Campbell.²¹
23. *Idem*. Observations on radical surgery for lesions of pancreas. *Surg., Gynec & Obst.* 82:623-631, 1946.
24. Brunschwig, A. *The Surgery of Pancreatic Tumors* 421 pp. H. Louis, C. V. Mosby Company, 1942.
25. Waugh, J. M., and Clagett, O. T. Resection of duodenum and head of pancreas for carcinoma. *Surgery* 20:224-232, 1946.
26. Dennis, C., and Varco, R. L. Neoplastic biliary obstruction. *Supp.* 20:72-81, 1946.
27. Clagett, O. T., and Hawkins, W. J. Cystic disease of liver. *Ann Surg.* 123:111-118, 1946.
28. Flynn, J. E. Pyogenic liver abscess: review of literature and report of case successfully treated by operation and penicillin. *New Eng J Med.* 234:403-407, 1946.
29. Gatch, W. D., Batterbury, J. S., and Wakim, K. G. Treatment of cholecystitis. *J. A. M. A.* 132:119, 1946.
30. Glenn, F., and Heuer, G. J. Surgical treatment of acute cholecystitis. *Surg., Gynec & Obst.* 83:50-54, 1946.
31. Wallace, R. H., and Allen, A. W. Acute cholecystitis. *Arch. Surg.* 43:762-772, 1941.
32. Johnston, G. A., and Ostendorp, J. E. Cholecystitis with perforation. *Arch Surg.* 53:1-12, 1946.
33. Hicken, N. F., and Coray, Q. B. Spontaneous gastro-intestinal fistulas. *Surg., Gynec & Obst.* 82:723-730, 1946.
34. Goldman, B., Jackman, J., and Eastman, R. H. Management of post-operative choledocholithiasis: another use for solution G. *Surg., Gynec & Obst.* 81:521-524, 1945.
35. Hudson, P. B., and Johnson, P. P. Hemorrhage from gall bladder. *New Eng J Med.* 234:438-441, 1946.
36. White, F. W., and Jankelson, I. R. Gastro-intestinal hemorrhage: a disease of gall bladder. *New Eng J Med.* 205:793-797, 1931.
37. Norgore, M. Traumatic rupture of gall bladder: case reports and notes on choleperitonium. *Ann Surg.* 123:127-134, 1946.
38. Sanders, R. L. Indications for and value of choledochoduodenostomy. *Ann Surg.* 123:847-858, 1946.
39. Lahey, F. H. Discussion of Sanders.³⁸
40. Flickinger, F. M., and Masson, J. C. Reconstructive operations for benign stricture of bile ducts. *Surg., Gynec & Obst.* 83:24-36, 1946.
41. Pearce, H. Unpublished data.
42. *Idem*. Benign strictures of bile duct. *Surg., Gynec & Obst.* 83:509, 1946.
43. Peterson, F. R. Reformed gall bladder: review of 42 cases. *J. Int. State M. Soc.* 36:134-138, 1946.
44. Guyton, W. L. Double gall bladder. *Am J Surg.* 72:116-120, 1946.
45. McLaughlin, E. F. Choledochus cyst. *Ann Surg.* 123:1047-1061, 1946.
46. Shallow, T. A., Eger, S. A., and Wagner, F. B., Jr. Congenital cystic dilatation of common bile duct: follow-up on previously reported case and report of additional case. *Ann Surg.* 123:119-126, 1946.

DR MALLORY Dr Taylor, you saw this patient. Will you give your opinion?

DR. TAYLOR When I saw this patient on the Orthopedic Service, my reasoning was much the same as that of Dr Sosman. I examined the vessels at the ankle closely with the stethoscope. If Dr Van Gorder had not gone out so flat-footedly for synovialoma I should not have considered any other tumor with such enthusiasm.

DR SOSMAN Why did you think it was not synovialoma?

DR TAYLOR I thought that there was more calcification than there should be in a synovialoma.

DR SOSMAN In Jönsson's article some of the illustrations reveal calcification in the tumor.

DR TAYLOR They do, but not so much as that in his case.

DR SOSMAN I agree with you that there is generally little or no calcification.

DR TAYLOR Do you think that the long duration argues against that type of tumor?

DR SOSMAN I do not believe so. Synovialomas may have a low degree of malignancy. This tumor was of six years' duration, with a sudden exacerbation of growth. Synovialomas may begin as benign or slowly malignant tumors.

DR MALLORY I am forced to disagree. In our experience, synovialomas have been among the most malignant tumors.

DR SOSMAN In young people they are quite malignant but not in old people. If the tumor had been present for ten years and had been extremely malignant metastases would certainly have occurred by the time of admission.

DR TAYLOR I agree with Dr Mallory. I cannot imagine a malignant tumor that existed so long without dissemination, however.

DR SOSMAN Synovialomas are rare at this age.

DR MALLORY What does Dr Lingley think about it?

DR JAMES R. LINGLEY The x-ray appearance is consistent with that of synovialoma. But I agree that such a tumor is rare at the age of this patient. All the cases I have seen have occurred in young patients.

DR. SOSMAN I should have mentioned a chondrosarcoma, which almost always arises on an osteochondroma and in which the original bony pedicle is visible somewhere around the joint. I do not remember a case in which chondrosarcoma arose from the joint cartilage itself. It must be considered because cartilage is one of the main structures of the joint. Cartilage is an end product, a secondary type of cell differentiation, and a tumor might start from embryonic or fibroblastic tissue and develop into cartilage. I should like to add chondrosarcoma to the mesothelial group, which could all be called synovialomas.

DR MALLORY Will you tell us the operative findings, Dr Barr?

DR BARR I tried to steer a middle course between Dr Van Gorder and Dr Taylor in the diagnosis. I was not sure what the diagnosis was. I thought of all these things but did not commit myself beyond the fact that I considered this a tumor and not a Baker cyst. The exposure was made through a posterior incision. A hard mass was found about the size of a small orange or lemon, in exactly the situation where one would find a Baker cyst. It was somewhat lobular and irregular and of hard, rubbery consistence. It was excised and was found to communicate with the joint by a small pedicle. I had hoped that we could do an excision of the whole tumor, whatever it was, and therefore had not opened it for biopsy. The dissection planes opened freely and easily, exposing the whole tumor. When the joint at the base of the pedicle was opened, three small, free fragments of tumor came out of the joint. We noted at that time that we had not been successful in excising the tumor completely.

CLINICAL DIAGNOSIS

Malignant tumor of right knee

DR SOSMAN'S DIAGNOSIS

Synovialoma (mesoblastoma)

ANATOMICAL DIAGNOSIS

Chondroma of right knee

PATHOLOGICAL DISCUSSION

DR MALLORY The specimen that was resected had the characteristic gross appearance of a chondroma. It was hard but also elastic, white and glistening. Histologically it consisted of well differentiated cartilage with a good deal of intercellular matrix and comparatively few cells. The appearance was completely benign from the histologic point of view. How a chondroma could arise in this spot, where there is normally no cartilage, is an interesting speculation. It may have been secondary to metaplastic cartilage formation. Occasionally, inside the knee joint, extensive change of the synovial tissue into cartilage occurs. The three tiny fragments within the knee joint slightly suggested that possibility. On the other hand it is difficult to understand how a process of that sort could have produced a large tumor external to the joint cavity. It is true that this man had had a lacerating injury of the knee in childhood and may have had a slightly deficient posterior capsule. I called it a chondroma and assumed that it must have arisen from a metaplastic process — a new formation of cartilage in the joint capsule. Cartilage can form from fibrous tissue in innumerable parts of the body and sometimes forms visibly peculiar areas.

than the tumor in this case and usually contain phleboliths, particularly if they are venous angiomas. Lipomas usually show characteristic diminished density on x-ray examination when they are in or between the muscles and fascia, but they do not show the increased radiability if they are in the subcutaneous tissue, where they are surrounded by fat. Fibromas could conceivably originate from synovial tissue and therefore be regarded as synovial tumors.

DR GRANTLEY W. TAYLOR: The knee was listened to, nothing abnormal being heard, and there were perfectly normal pulsations in the ankle vessels. There was no bruit or pulsations over the mass.

DR SOSMAN: Arteriovenous aneurysms have either bruit or arterial pulsations or both in practically all cases.

I have not seen tuberculomas behind the knee, although they can occur anywhere. But the absence



FIGURE 1 *Roentgenogram of Right Knee.*

An aneurysm of the popliteal artery should be considered, and they contain calcium, particularly the arteriovenous aneurysm. These usually follow a penetrating wound, however, in which there has been an actual cutting of the artery and vein, resulting in arteriovenous communication, and produce channel-like structures. This case might possibly fit that description. In this situation that obsolete instrument, the stethoscope, might come into play. Was the stethoscope used on this knee?

of tuberculosis in the chest helps to rule out that diagnosis. Another possibility is a giant-cell tumor of the tendon sheath, which may occur anywhere but much more frequently around the wrist. It may be lobulated and may contain flecks of calcium.

In summary, I think that this was a mesoblastoma that arose not from endothelial or epithelial cells but from some of the mesoblastic structures. If I had not been invited to discuss this case I should have called it a synovialoma.

DR MALLORY Dr Taylor, you saw this patient. Will you give your opinion?

DR TAYLOR When I saw this patient on the orthopedic Service, my reasoning was much the same as that of Dr Sosman. I examined the vessels in the ankle closely with the stethoscope. If Dr Van Gorder had not gone out so flat-footedly for synovialoma I should not have considered any other tumor with such enthusiasm.

DR SOSMAN. Why did you think it was not synovialoma?

DR TAYLOR. I thought that there was more calcification than there should be in a synovialoma.

DR SOSMAN. In Jönsson's article some of the illustrations reveal calcification in the tumor.

DR TAYLOR. They do, but not so much as that in his case.

DR SOSMAN. I agree with you that there is generally little or no calcification.

DR TAYLOR. Do you think that the long duration argues against that type of tumor?

DR SOSMAN. I do not believe so. Synovialomas may have a low degree of malignancy. This tumor was of six years' duration, with a sudden exacerbation of growth. Synovialomas may begin as benign or slowly malignant tumors.

DR MALLORY. I am forced to disagree. In our experience, synovialomas have been among the most malignant tumors.

DR SOSMAN. In young people they are quite malignant but not in old people. If the tumor had been present for ten years and had been extremely malignant metastases would certainly have occurred by the time of admission.

DR TAYLOR. I agree with Dr Mallory. I cannot imagine a malignant tumor that existed so long without dissemination, however.

DR SOSMAN. Synovialomas are rare at this age.

DR MALLORY. What does Dr Lingley think about it?

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DR SOSMAN There was no sign of invasion? Did the tumor shell out perfectly smoothly?

DR BARR Yes, just as smoothly as a Baker cyst

DR SOSMAN Was it attached to the cartilage of the knee joint?

DR BARR No, just to the capsule itself Was that true histologically?

DR MALLORY Yes

DR BARR Were the lines of excision beyond the tumor itself so far as you could determine?

DR MALLORY Yes

DR JOSEPH C AUB What is the function of the knee at present?

DR BARR It was markedly limited before the tumor was removed, the patient had practically no motion, obviously because the posterior tibial nerve lay directly over the tumor and on attempts at extension it was spread so that he could not extend the leg on account of the pain and could not flex it because of the tumor mass He has gained some motion but has still far from normal function of the knee

CASE 33042

PRESENTATION OF CASE

A sixty-six-year-old Greek textile worker entered the hospital because of anorexia and weight loss

Eighteen years before entry the patient had had a six-day episode of abdominal swelling Seven years later he had had a short period of illness associated with nausea Four years before admission an attack of sharp epigastric pain had occurred Two years later, following a tooth extraction, he developed chilly sensations and began to lose weight X-ray studies were said to have shown gallstones, and fourteen months before entry a cholecystectomy was performed at another hospital The gall bladder was chronically inflamed and thick walled, and contained several dark stones, the largest of which measured 1.2 cm in diameter The wound drained, and healing required five months, during which the patient developed jaundice and ran a slight fever Six months before entry he was readmitted to the hospital because of jaundice, pain in the chest and epigastric region, and vomiting for three days At that time examination of the blood showed a red-cell count of 3,440,000, with a hemoglobin of 62 per cent, and a white-cell count of 8500, with 77 per cent neutrophils The icteric index was 30 units The patient was placed on a low-fat, high-vitamin diet but continued to go downhill About once every week he had a shaking chill lasting two or three hours The urine became dark Four months before entry a laparotomy at the other hospital revealed a large liver Multiple punctures with a long needle failed to reveal an abscess The common duct was palpated, but no stones were found Postoperatively, the jaundice decreased slightly, but the

anorexia and weekly chills continued Frequent episodes of nausea and vomiting also began A month before entry the abdomen began to swell

The patient had had malaria when a youth He drank alcoholic beverages about once a week, but never to excess

Physical examination revealed a markedly jaundiced man, with evidence of recent weight loss There were soft axillary lymph nodes, measuring up to 1 cm in diameter A few crackling inspiratory rales were heard at the right base The heart was not enlarged The abdomen was distended, with a definite fluid wave The liver was moderately tender, and its edge was felt two fingerbreadths below the costal margin The prostate was smooth and of twice the normal size The right knee was ankylosed in full extension

The temperature was 99.4°F, the pulse 100, and the respirations 26 The blood pressure was 130 systolic, 64 diastolic

Examination of the blood revealed a red-cell count of 3,500,000, with a hemoglobin of 9.0 gm, and a white-cell count of 10,600, with 81 per cent neutrophils The serum phosphorus was 3.5 mg, the non-protein nitrogen 30 mg and the total protein 6.9 gm per 100 cc, with an albumin-globulin ratio of 0.6, the alkaline phosphatase was 27.5 Bodansky units per 100 cc The van den Bergh reaction was 4.3 mg per 100 cc direct and 5.7 mg total The prothrombin time was 23 seconds (normal, 19 seconds) The urine gave a +++ test for albumin and a +++ test for bile The stools were formed, tan and guaiac negative

X-ray films of the chest revealed a slightly elevated diaphragm on the right A plain film of the abdomen showed slightly dilated loops of small bowel with homogeneous, ground-glass density

A skin test with echinococcal antigen was negative

The patient received several blood transfusions, a high intake of glucose orally as well as intravenously and 24,000 units of penicillin every three hours At first there was a striking fall in temperature, but on the sixth hospital day, the temperature resumed a spiking course, frequently going above 102°F On the seventeenth hospital day a paracentesis was performed, and 3300 cc of yellow fluid with a specific gravity of 1.008 was withdrawn

Another gastrointestinal series showed rather extensive curling of the lower esophagus but no definite evidence of varices The duodenum and upper small intestine were within normal limits, but the patient was examined only in the horizontal position

On the nineteenth hospital day an operation was performed

DIFFERENTIAL DIAGNOSIS

DR ARTHUR W ALLEN Dr Schatzki, do you suppose that the x-ray films will help me?

DR RICHARD SCHATZKI I am afraid they will not of much help. The plain film of the abdomen at the time of admission shows slight dilatation of the small bowel and increased density of the whole abdomen, as one would expect with fluid in the abdomen. On the chest film in the lateral view, there is, in addition to what is stated in the report, slightly more lobulation than is seen in the average patient. Lobulation of the diaphragm does not necessarily mean anything so far as disease is concerned, but in a patient with liver disease I should make a mental note of it but should usually not record it. Perhaps I am leading you astray. I do not know the answer.

DR ALLEN Neither do I.

DR SCHATZKI These films show a small hiatus hernia and a slightly tortuous esophagus, as one would expect with a high diaphragm. There is some curving of the esophagus, and the folds look thicker than they should be, even considering the high position of the diaphragm. In a patient with a tortuous esophagus, the differentiation of folds and varices is rather difficult and sometimes impossible to make, unless the varices are definite. They are certainly not definite in these films.

DR ALLEN We have a clear-cut story that ought to be correct so far as the findings at operation are concerned, in spite of the fact that this man was probably born in Greece, where echinococcal disease is frequent. He was undoubtedly studied with that point in view, and it is possible that the second exploration in the other hospital was performed to demonstrate an echinococcal cyst.

A disturbing feature about the history from the standpoint of diagnosis is the finding in the peritoneal cavity of a large amount of yellow-stained fluid with a low specific gravity. One must assume that this fluid was not bile but was possibly slightly bile stained, as all the tissue fluids were, and that it did represent a true ascites. That is unusual in the type of situation that I believe existed in this case. Free fluid is often found in patients who are chronically ill, particularly if they are ill with a disease that affects the liver. The negative x-ray examination for esophageal varices and the fact that there was no blood in the stools are evidence that this was not a simple cirrhosis of the liver of an independent nature. Of course, this patient had cirrhosis, which was probably a biliary cirrhosis on the basis of obstruction in the bile duct. I cannot see any connection between the early history of malaria and the condition as it is presented in the record.

The history goes back eighteen years, with a short episode of abdominal distress and swelling, lasting six days, that could have been the initial onset of difficulty with gallstones. There was another

episode of nausea eleven years before entry, and an attack of sharp epigastric pain, which is compatible with real biliary colic, seven years later. The difficulty starting two years before entry, following the tooth extraction, represented the acute phase of the process—the tooth extraction, in my opinion, had nothing to do with the weight loss and the chills and fever, which indicate a cholangitis on the basis of infection, primarily originating in the gall bladder itself and finally involving the bile ducts. It would be extremely difficult to visualize this picture on the basis of any nonsurgical disease. The only point that bothers me is the ascites. The chance that this illness was caused by a tumor in the region of the head of the pancreas or the papilla of Vater is not great, although such a tumor, of course, would account for the ascites better than the situation that I believe existed.

The fact that the stools were tan interests me a little. No chemical test for bile is recorded. A deeply jaundiced person could have a stool that might be called tan because all the fluids in the body are naturally bile stained, but I believe that we must accept the fact that some bile was getting into the gastrointestinal tract, although not much, as in many patients with cholangitis with complete or almost complete obstruction. A small amount of bile seeps through an opening so small that on the operating table one cannot actually visualize it and wonders how any bile can get through at all.

At the first operation, when the gall bladder was removed, stones were found in a chronically thickened gall bladder. The important feature to me is that drainage through the wound continued for five months after the cholecystectomy. We are not told the nature of the fluid drained, but we must assume that it was bile. As this drainage to the outside began to decrease, the patient became jaundiced and began to have chills once a week. So long as bile was draining to the outside these chills probably did not take place, and he might have been in a fairly reasonable state of health, although the anorexia and weight loss were probably not corrected because we have no information that the lost bile was returned in any way to the gastrointestinal tract.

The causes of jaundice with cholangitis following cholecystectomy may be two: the first is an overlooked obstruction in the common bile duct, which may allow a certain amount of bile to get into the intestinal tract and which may occur with no evidence of jaundice. When there are a number of stones, bile seeps around them as water does in a stone drain in a wet field, and jaundice does not occur. A single stone or stones headed by a large stone in the ampulla are likely to cause complete jaundice and to allow less bile to seep through.

Cases of tumor in the region of the head of the pancreas often have intermittent phases of jaundice, and a certain amount of bile frequently gets into the gastrointestinal tract in spite of obstruction. The other cause (and I am sure that I was assigned this case because it was hoped that I should arrive at this conclusion, which is probably wrong) is that at the time of the cholecystectomy an injury to the common duct occurred. Unfortunately, this takes place often enough so that in a clinic such as this there are usually one or two such patients who have been sent in to have something done about the situation. This patient must have had an obstruction of some sort or an injury to the duct for bile to drain for five months after cholecystectomy. The gradual onset of the final condition following the original operation makes one wonder whether a tenting of the common bile duct, with a ligature around it, finally produced complete or nearly complete obstruction of the duct. The type of injury that usually precipitates early recognition is one in which the common bile duct is mistaken for the cystic duct and a large portion of it is removed.

I therefore conclude that this man had an injury to the common bile duct, and that he had, of course, biliary cirrhosis due to the obstruction and cholangitis in addition to or as a result of the injured duct.

DR TRACY B. MALLORY: Will you tell us the opinion on the wards, Dr. Volwiler?

DR WADE VOLWILER: There were three things we argued about considerably on the medical service before exploration. The most troublesome was the problem of ascites, which also bothered Dr. Allen. It was certainly a transudate. We did not believe that a biliary cirrhosis was necessarily present. The albumin-globulin ratio, although considerably reversed, was not lower than that in prolonged obstructive jaundice and malnutrition without biliary cirrhosis. We have seen several cases in the last few years in which an inflammatory process in the region of the gall bladder or a pyelophlebitis has occurred with massive ascites. Dr. Linton's theory was that a partial lymphatic block allowed localization of fluid in that area. We have seen several patients with complete biliary obstruction, with clay-colored stools of four to six months' duration, who at operation or at post-mortem examination showed no histologic signs of biliary cirrhosis. I think that there is no way of predicting whether or not such cirrhosis will be found, unless there are secondary xanthomas. I am sure that the element of infection is important in its production, and I suppose that in this case it would be a safe bet.

We were also uncertain whether or not there were hepatic abscesses, with the high temperature and the chills and fever. The liver was definitely tender to palpation, which we thought was another point in favor of abscess, although the white-cell count was always much lower than that in most cases.

DR MALLORY: Did you assume that the liver was large?

DR VOLWILER: We thought it was somewhat larger than normal, but we see enlarged livers merely from bile stasis, without any additional intrahepatic fibrosis.

DR ALLEN: I might add that I have seen a number of these patients with injuries to the bile duct who finally came in with a tender liver, not all are tender, but some definitely are.

CLINICAL DIAGNOSIS

Common-duct stone

DR ALLEN'S DIAGNOSES

Common-duct injury
Biliary cirrhosis
Cholangitis

ANATOMICAL DIAGNOSES

Defect of common bile duct, postoperative
Cholangitis
Biliary cirrhosis
Erosion of intrahepatic branch of portal vein, with hemorrhage
Intrahepatic cholelithiasis
Bronchopneumonia
Recent operative wounds, choledochojejunostomy, jejunojejunostomy

PATHOLOGICAL DISCUSSION

DR MALLORY: At operation only insignificant remnants of the common bile duct could be found. It was necessary to do an anastomosis of a loop of jejunum to the right hepatic duct practically within the hilus of the liver. This was carried out successfully, although with considerable difficulty, and a series of adjusting anastomoses were made in the small intestine. A drain to the exterior was also placed in the hepatic duct. Following operation the patient did well for about two weeks and then began to have a series of massive hemorrhages through the drainage tube in the abdominal wall and also in the bowel. He passed several tarry stools. On two occasions he bled himself out almost completely, passing at one time into a stage of unconsciousness. He was revived with multiple transfusions. Two days after one of these episodes he was up in a wheel chair again and, for the moment, in excellent condition. He had a final massive hemorrhage, however, and died.

At autopsy we found that a large segment of common bile duct was missing. Only 2 or 3 cm. of the duct remained next to the duodenum, and a large stone, nearly 2 cm. in diameter, was found impacted in the ampulla. Above the point where the duct had

transsected additional stones were found in
nches of the hepatic duct throughout the left
e of the liver. The intrahepatic bile ducts were
markedly dilated in both lobes, there were multiple
stones in the ducts of the left lobe, but none in the
ducts of the right lobe. There was an extremely
severe biliary cirrhosis — one of the most marked
that I have ever seen. There was also a marked
cholangitis extending throughout all the radicles
of the biliary system. It was an inflammatory
process extending from the infected bile ducts that
had eroded into a branch of the portal vein within
the liver and had produced the fatal hemorrhage.
One of the surprising facts at autopsy was that,

in spite of the long-continued obstructing jaundice
and the multiple episodes of hemorrhage into the
ducts, the kidneys were almost perfectly normal.
There was terminally a rather extensive broncho-
pneumonia.

DR ALLEN: Was there any evidence that the ero-
sion between the hepatic duct and the branch of the
portal vein had been produced by the tube used at
the anastomosis?

DR MALLORY: As I read the record, I do not be-
lieve so.

DR ALLEN: I do not believe that we have ever
seen such erosion in all the cases in which we have
repaired the bile duct.

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

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MATERIAL should be received not later than noon on Thursday, two weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

CONTROL OF TYPHOID FEVER AND TUBERCULOSIS

THE effectiveness of the application of sound public-health principles is no better illustrated than by the decrease in deaths from typhoid fever that has occurred in the large cities of the United States during the last thirty-six years. In 1945, according to the most recent report,¹ there were only 80 deaths in seventy-eight cities with a total population of 35,895,638, whereas in 1910 there were 4637 deaths in the same cities, whose total population at that time was 22,573,435. The respective death rates per 100,000 are 0.22 and 20.51, a difference of nearly a hundredfold. In 1945, fifty-six cities reported no deaths, thirty-one had death rates varying between 0.1 and 0.9, five between 1.0 and 1.9, and one between 2.0 and 4.9, whereas in 1910, of the seventy-

seven cities whose statistics are available, two had rates ranging from 5.0 to 9.9, and in the remainder the rates were 10.0 and over. In the period 1941-1945, the rates according to geographical divisions are as follows: 0.14, New England; 0.16, East North Central and West North Central; 0.17, Middle Atlantic; 0.23, Mountain and Pacific; 0.54, South Atlantic; 0.57, East South Central; and 0.89, West South Central.

Owing to proper control of water supplies and sewage disposal and to regulations governing the distribution of milk and other foodstuffs, including the handling of food, epidemics of typhoid fever are essentially things of the past. The cases that do occur, particularly those in areas with low mortality rates, are usually due to direct or indirect contact with an unrecognized typhoid carrier. In Massachusetts, for example, there are approximately 170 recognized typhoid carriers at the present time, and it is estimated that there are probably in the neighborhood of 1000 unrecognized carriers. Although it is possible to minimize the risk of contagion from those who are known to excrete typhoid bacilli from the gastrointestinal or urinary tract, obviously nothing can be done to control the spread of infection by the unrecognized carrier. Over the course of years, however, the number of such persons is certain to approach zero. In spite of the fact that the subcutaneous injection of typhoid vaccine results in a reasonably effective immunity against typhoid infection, there appears to be no indication for its use, unless a person resides in or plans to visit an area in which the disease is endemic or temporarily epidemic.

This present mode of infection in typhoid fever parallels that for tuberculosis, in that both are largely contracted from persons with unrecognized infections. Now that tuberculosis has been practically eliminated from dairy herds and the milk from the occasional tuberculous cow is rendered innocuous by pasteurization, the spread of this disease depends chiefly on contact with human tubercle bacilli from persons having recognized or unrecognized open tuberculous lesions.

Fifty years ago, when infection with tuberculosis was almost universal, little could be accomplished in limiting the foci of infection. With a drop of some

er cent in the death rate, however, the picture radically changed and, as in typhoid fever, the serious case has become the primary object of attack. In tuberculosis only the open case is a source of infection, and the continued, steady decline of disease in this country during the last seventy-years is convincing evidence that, on the whole,

the case is giving rise to less than one new case. Frost² has well pointed out, this can only mean that the biologic balance is against the survival of tubercle bacillus and, if this balance can be maintained, that the ultimate eradication of tuberculosis is a possibility.

As the incidence of tuberculosis decreases, concentration on the open case will yield increasing returns. This means early diagnosis and prompt hospitalization of active cases and routine x-ray examination of all family contacts, especially adults. Our experience has shown, however, that, even under the most favorable conditions, not over half the new cases can be traced to direct contact, the rest must be spread wide to be really effective. This has become practical with the development of photofluorography during the past few years. Under the selective Service system nearly 20,000,000 young men and women in this country were screened with x-ray films of the chest and approximately 1.25 per cent were rejected because of the findings. On the basis of discharge examinations it is estimated that the incidence of tuberculosis in the armed forces of the United States in World War II was only about one-tenth of that in World War I. At the same time the 2,000,000 workers in arsenals, shipyards and other industries received routine x-ray examination, largely through the efforts of the United States Public Health Service.

Facilities for routine x-ray examination of household contacts of tuberculous patients are now available to physicians in nearly all states. Many state health departments, often with the assistance of voluntary associations, have embarked on programs for the routine examination of industrial workers. Some have already begun mass x-ray examination of the adult population of entire communities for the discovery of unrecognized foci of infection. Hospitals offer a fertile field for this type of case finding, both for the detection of unsuspected cases

among patients and for the protection of nurses and other employees.

The problem of control in tuberculosis is more complex than that of typhoid fever, but the principles are becoming more and more similar. In tuberculosis, individual resistance plays an important but still largely unmeasured role and the influence of environment was again tragically demonstrated in invaded countries in the recent war. When, in addition to routine examination of suspects and household contacts, mass x-ray screening of the adult population is provided, as well as adequate sanatorium facilities for the isolation and treatment of all active cases, and when nations have learned how to live for more than one generation without war, tuberculosis should become as truly preventable as typhoid fever.

REFERENCES

- 1 Special Article. Typhoid in large cities of United States in 1945, thirty-second report. *J. A. M. A.* 131:817-821, 1946.
- 2 Frost, W. H. Outlook for eradication of tuberculosis. *Am. Rev. Tuberc.* 32:644-650, 1935.

FULTON'S HARVEY CUSHING

MEDICINE in general has been unusually fortunate in the biographers of her worthies. *The Life of Sir William Osler*, by Harvey Cushing, a full two-volume estimate of Osler and his influence on Canadian, American and English medicine, published in 1925, set a standard never before reached in medical biography in this country and indeed seldom equaled in all the history of physics. One can only compare it with Stephen Paget's discriminating study of Victor Horsley or with Humphry Rolleston's thoughtful biography of Clifford Allbutt, to mention only two outstanding modern examples. As the Cushing volume is so richly autobiographical, there comes to mind also those more personal reminiscences of contemporary physicians, such as Hans Zinsser's appealing *As I Remember Him*. *The biography of R. S. Ramón y Cajal's penetrating Recollections of My Life*, Bland-Sutton's sprightly *The Story of a Surgeon*, August Forel's *Out of My Life and Work* and, in a lighter vein, *The Horse and Buggy Doctor* by Hertzler and *Sands of Time* by Purves-Stewart. To these of recent date should be added the fine tribute to Théodore Tronchin by Henry Tronchin and the memorable account of

William Henry Welch by Simon Flexner and his gifted son James Thomas Flexner

To this brief list, fully recognized as incomplete, must now be added the biography of Harvey Cushing by John F. Fulton. Few biographies are more satisfying than this competent life. Much was told by Cushing himself, and a mosaic, based on such original sources, has been judiciously fitted into a full portrait by his skilful biographer.

A review of the book appears elsewhere in this issue of the *Journal*. The volume is a worthy contribution to medical biography, and physicians, medical students and indeed the lay public should find inspiration and a stimulus to greater things in reading the life of the outstanding surgeon of his age and a medical pioneer of no mean ability.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

PAINTER — Charles F. Painter, M.D., of Brookline, died January 6. He was in his seventy-eighth year.

Dr. Painter received his degree from Harvard Medical School in 1895. He was formerly dean of Tufts College Medical School, librarian of the Boston Medical Library, for many years a member of the editorial board of the *Journal of Bone and Joint Surgery* and editor of the *Yearbook of Orthopaedic Surgery*. He was a fellow of the American College of Surgeons, an eminent member and former president of the American Orthopaedic Association and an emeritus member of the American Academy of Orthopaedic Surgeons.

His widow, a son and a daughter survive.

STONE — George H. Stone, M.D., formerly of Worcester, died January 4. He was in his sixty-sixth year.

Dr. Stone received his degree from Bowdoin Medical School in 1908. He was formerly superintendent of Worcester Memorial Hospital and was a fellow of the American Medical Association.

NEW HAMPSHIRE MEDICAL SOCIETY

ROCKINGHAM COUNTY NEWS

A leaflet *Rockingham County Medical Society News* is now being sent out monthly from the office of the secretary, Dr. Donald W. Leonard, of Exeter. The December, 1946, copy contains a short report of the annual meeting, an account of a meeting of the Women's Auxiliary, information from the secretary of the New Hampshire Medical Society, a list of the officers of the county society and a note regarding the annual meeting of the New Hampshire Medical Society.

By this means, the officers of the Rockingham County Medical Society plan to keep its members informed concerning news within the county and to carry announcements, with the hope that this will stimulate greater interest in the affairs of the society, particularly its regular meetings.

NOTE

The following New Hampshire physicians were recently appointed fellows in the American College of Surgeons: William P. Clough, Jr., New London, Edward D. Hagerty, Nashua, B. Read Lewin, Claremont, and Raymond R. Perreault, Rochester.

BOOK REVIEW

Harvey Cushing: A Biography By John F. Fulton, M.D. 754 pp. Springfield, Illinois: Charles C. Thomas, 1946. \$5.00.

Harvey Cushing, neurosurgeon, author, diarist, bibliophile and scholar, whose name ranks with those of William Osler, William H. Welch and others, stands out as one of the great physicians of our time. He was quite possibly the most distinguished graduate of the Harvard Medical School, certainly one of the greatest of American surgeons and, without question, a man whose influences in more than one field of medicine will have enduring recognition. To have virtually developed a new department of surgery, to have written the foremost biography of a contemporary medical figure, — a book widely proclaimed both in and out of his profession, — and to have greatly enriched the fields of medical history and science are accomplishments of no mean order. Harvey Cushing did each of these and, in addition, molded the lives of countless young men who later, in turn, have made no inconsiderable advancements in the progress of medicine. Not the least of those he trained is his talented pupil and friend of his later years, a distinguished professor of physiology and the author of his biography. Harvey Cushing, long anticipating that an account of his eventful life might be of use to future students of medicine, kept voluminous notes and diaries, almost writing his own biography by the daily activity of his pen. Few men have left a larger accumulation of pertinent material for a competent biographer to sift, or more remarkable papers and drawings on which the latter could base the reactions of his subject to the events of his time.

Harvey Cushing was born in Cleveland, Ohio, on April 8, 1869, the descendant of an English family that came to New England in 1638. His grandfather, Erastus Cushing, M.D., the son of a country doctor, emigrated by the Erie Canal to the Western Reserve of Connecticut in 1835, and there, in Cleveland, his father, Henry Kirke Cushing, M.D., was brought up. The latter was a shy, somewhat austere and puritanical person, although highly regarded as a practitioner of gynecology and obstetrics. With the heavy responsibilities of a large family, Dr. Cushing was frugal to the point of penuriousness. Often silent and secretive for days, speaking to no one in his family, he led at times a somewhat somber life. Harvey Cushing's mother, on the other hand, was even-tempered, forceful and kindly, with humor, grace and an inner gaiety of spirit. Some of these qualities, as well as some from his father, Harvey Cushing inherited in full measure. He was the youngest in a family of ten children, only seven lived to maturity. One brother also became a physician, and the others were supplied by their thrifty father with splendid educations. The eldest graduated from the Harvard Law School and practiced his profession in Cleveland for many years, another graduated from Cornell University and became a geologist of note, the older brother who became a physician went to Cornell and then to the Harvard Medical School, and Harvey was sent to Yale and then to the Harvard Medical School. Surely few fathers have given their sons better educational opportunities than did the penurious Cleveland practitioner.

Harvey Cushing's career at Yale was that of an undistinguished but creditable scholar, a superb athlete, particularly brilliant in baseball and adept at gymnastics, and a popular boy who was elected to the proper clubs in spite of his father's disapproval of both intercollegiate athletics and college societies. Cushing's ability to make sketches and his powers of description were already discernible in his college years. Preserved are the diagrams of his first quarters in New Haven and a striking description, in a letter to his mother, of the blizzard of 1888.

Turning to medicine, Cushing entered the Harvard Medical School in 1891. The high stone steps of the building (now part of Boston University) on Boylston Street in Boston tempted him to repeat his performance off the steps of the Yale gymnasium, and with a lighted cigarette in his mouth he turned a back somersault, landing upright on the bare sidewalk with the cigarette still going. This no doubt made the transition from New Haven to Boston less difficult than he had expected, but Cushing soon developed an uneasiness about Harvard that he never quite overcame. He soon became heavily involved in his studies, however, and by the second half of his second year he was etherizing for Dr. Warren. One

his first patients died under the anesthetic, a profound shock to the sensitive young medical student. Later, he became depressed with frustrations and a feeling of inadequacy, these he overcame by dint of hard work, which won for him a surgical internship at the Massachusetts General Hospital. He was regarded by his friends as the ablest man in his class. While a student he, with Amory Codman, devised a method for recording the temperature and pulse of a patient during etherization. When serving as an intern, he and Codman again collaborated, this time on x-ray photographs. In the spring of 1896 they purchased a crude machine and took pictures, activating their x-ray tube by a hand-driven electric machine and using exposures up to twenty minutes to get a clear plate. Cushing, even in those days, was a perfectionist, difficult to work with and ambitious almost to a point of intolerance, arousing many animosities among his fellow workers. He was also critical of his surgical teachers, writing at "these men operate about the way a commercial traveler takes breakfast at a lunch counter."

In 1896 Cushing went to the Johns Hopkins Hospital to serve as an assistant resident in surgery under Dr. William Halsted. There he remained for thirteen years. Bringing with him his x-ray apparatus from Boston, in 1896 Cushing made the first x-ray films taken at Hopkins. A patient with a bullet in the cervical spinal cord interested him and, using photographs of x-ray films as illustrations, he published his first original piece of writing in 1897. Cushing soon became a great favorite with the patients in the wards—but not always with the nurses or his fellow members of the staff. Dr. Halsted was often sick, and Cushing saw little of him during his three years as resident. He thus had more responsibility than most young surgeons and more opportunity for developing his own technique. Following Halsted's work on cocaine infiltration, Cushing began a series of studies on block anesthesia in 1898. When came a pioneer development in the handling of patients with typhoid perforations and a paper on gonococcal peritonitis.

Going abroad in 1900, Cushing went to Berne, where he did experimental work in Kronecker's laboratory and attended Theodor Kocher's clinic. He carried his experiences with animals in Kocher's laboratory, where he observed the brain through a small window in the skull to Mosso in Turin. There, using the same technic, he studied a man with a cranial defect. Seeing a model of Riva-Rocci's blood-pressure device in Pavia, Cushing promptly sketched it and brought a model back to Baltimore when he returned home. Most of his investigations at various centers were followed by papers, published in current journals. In some instances these had a bluntness and lack of diplomacy that caused considerable disconcertion among his senior men, who were accustomed to write papers in their own names that were based on the work of their pupils. Later came a productive month with Sherrington in Liverpool before returning to America.

Returning to Johns Hopkins Hospital in 1901, at the age of thirty-two, Cushing began practice, living next door to the Oslers, at 3 West Franklin Street. With Thomas B. Fitcher and Henry Barton Jacobs, he became one of the "latch-keyers" to the "man-next-door," William Osler, whose life he described many years later in the most successful medical biography of its time. He then developed a growing interest in surgery of the nervous system, spaced with experimental studies on blood pressure, courses in graduate instruction in general surgery and studies in the physiology of saline solution.

Cushing had long shown more than a casual interest in neurologic surgery, first at the Massachusetts General Hospital and later in his experimental researches abroad. At Hopkins his attention was directed to this special field of therapy through a simple operation for meralgia paresthetica on the astrophysicist Simon Newcomb, a long series of investigations on the Gasserian ganglion and a special assignment to this department of surgery under Dr. Halsted. By 1904 he was ready to make his first report as a "brain surgeon," and in 1908 he wrote the long chapter "Surgery of the Head" for Keen's *Surgery*. The operative mortality was so high in those days that Cushing at once turned to the problem of improvement in technic, devising the cranial tourniquet and new instruments. Also, he began his study of the pathology of brain tumors, noting their variation in recurrence and other features of their natural history.

From 1908 to 1912 came the period of the experimental work on the pituitary body, the development of suboccipital exposure for cerebellar tumors, trips to Europe, the first

operation on General Leonard Wood in 1910 and the publication of the pituitary monograph in 1912. Cushing had a curious way of setting up a theory and then making every effort to prove it, even when accumulated evidence showed that his theory was based on unsound premises. He was led astray regarding the finding of pituitary extract in the spinal fluid and never admitted that he was wrong, a curious foible in a man who had so many obvious virtues as an investigator. This caused some of his junior associates to waste valuable time in attempting to establish Cushing's original contention. The pituitary monograph, however, was characterized by the remarkable case histories, the discussion on acromegaly, gigantism and hypopituitarism, the microscopic studies and the development of the surgical approach to pituitary tumors—all contributions of major importance. As Osler remarked, it opened "several new chapters in cerebral physiology, to say nothing of metabolism."

In 1912 Cushing removed to the newly established Peter Bent Brigham Hospital in Boston as surgeon-in-chief and at the same time became the Moseley Professor of Surgery at Harvard University. Here he continued and greatly expanded his brain-tumor clinic, developed a new series of research problems, trained a long list of young students, interns and residents and made Boston a center for neurosurgery. His special field of endeavor was twice interrupted by war—first in 1915 when he led the Harvard Surgical Unit to Paris and secondly by his command of Base Hospital No. 5, which went overseas in 1917. His voluminous diaries were partly published in the book "From a Surgeon's Journal" in 1936. Back in Boston, his clinic ever expanding and the Society of Neurological Surgeons founded, Cushing turned to preparation of the Osler biography, his major literary work and possibly his greatest contribution to fame. The book, published in 1925, received wide acclaim and was awarded the Pulitzer Prize in 1926. Five more years brought his operations on brain tumor cases to over two thousand, and with the description of a new syndrome, pituitary basophilism, his active work in surgery drew to a close. His last operation occurred in August, 1932, at the age of sixty-three. Leaving Boston he settled happily in New Haven near his old and cherished Yale University, where he remained, developing a brain-tumor registry, exploring his library and making plans to leave it to the University, writing his bibliobibliography of Vesalius and, except for periods of great pain and distress, enjoying life to the utmost with old and new friends until his death in 1939.

His biographer has wisely kept a restraining hand on the more turbulent moments, and with studied care he has etched a portrait of Cushing without giving offense. Harvey Cushing was too great a man for some of his nimble jumps into controversy not to be overlooked, as he did so frequently himself. But, as with his famous backward somersault, he usually came up aright, with cigarette glowing and much justified applause for his audacity. In the intenseness of his life much was sometimes ruthlessly pushed aside, but he not infrequently showed the warmer side of his nature with equal or even greater fervor. So many acts of kindness went untold—medical students helped both financially and spiritually, friends made unexpectedly happy by unannounced visits, gifts on appropriate occasions and messages to those in distress. Few men have had a "harder" practice, for patients with brain tumors bring many problems to the neurosurgeon, often of a tragic nature. Cushing felt deeply and was profoundly touched by misfortune, as many a patient and friend can testify. His brusqueness, too, hid an essentially shy, sensitive nature, for at heart he was a deeply lovable person, driving himself and being driven by the environment he created to heights not often attained. He flew high and straight, maintaining an altitude of greatness throughout his life. In reading his skillfully written biography one never glimpses Cushing as "grounded."

The book is published in a fitting manner, finely printed and illustrated. Only two devoted friends, his biographer and the publisher, could combine to make a volume so representative of the man who meant so much to both of them. Modestly priced to fit the pocket of the medical student of the day, the book should be compulsory reading for every man and woman entering medicine as a profession. Poor indeed is the student who cannot gain from reading the life of one of America's finest products, a man who inspired his contemporaries as few others have done and who will continue to enrich the lives of those that come after him, thanks to this worthy volume.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Clinical Application of the Rorschach Test By Ruth Bochner, M.A., psychologist, Bellevue Psychiatric Hospital, New York City, and Florence Halpern, M.A., psychologist, Bellevue Psychiatric Hospital. Second edition, revised and enlarged. 8°, cloth, 331 pp. New York: Grune and Stratton, 1945. \$4.00.

The first edition of this book was well received when published a few years ago. Since that time the authors have added a considerable amount of material on this subject, one of the most frequently used tests in studying the field of personality. The authors believe that this test contributes materially to the subject in a manner that cannot be obtained through the medium of other techniques. The test, however, as they point out, has distinct limits. The book has become a standard text in its field.

Active Psychotherapy By Alexander Herzberg, M.D., Ph.D. 8°, cloth, 152 pp. New York: Grune and Stratton, 1945. \$3.50.

The author has a wide experience in the treatment of psychoneuroses, both in Germany and in England, and this book reflects his experience. Many case histories are given in some detail, along with facts on the technique of psychoanalysis and its value to psychiatry. The book is concise and practical, for it is based on the study of 500 cases over a period of twenty years.

The Osseous System. A handbook of roentgen diagnosis By Vincent W. Archer, M.D., professor of roentgenology, University of Virginia Department of Medicine. 8°, cloth, 320 pp., with 148 plates. Chicago: The Year Book Publishers, Incorporated. \$5.50.

This book has been written for the occasional radiographer and should therefore be considered a primer rather than a comprehensive text. In writing the work the author has taken advantage of mistakes that have been observed over a period of twenty years in a teaching position and in hospitals, as well as those made by individual physicians.

Skin Diseases in Children By George M. MacKee, M.D., professor of clinical dermatology and syphilology, New York Post-Graduate Medical School, Columbia University, and Anthony C. Cipollaro, M.D., associate in dermatology and syphilology, New York Post-Graduate Medical School, Columbia University. 8°, cloth, 448 pp., with 225 illustrations. New York: Paul B. Hoeber, Incorporated, 1946. \$7.50.

This book has been written chiefly for the general practitioner, and the second edition has been thoroughly revised to date. Special attention is given to methods of treatment that are suitable for the use of the family physician. Many new photographs and colored plates have been added.

Gastro-Enterology. Volume III. The Liver, Biliary Tract and Pancreas, and Secondary Gastro-Intestinal Disorders By Henry L. Bockus, M.D., professor of gastroenterology, University of Pennsylvania Graduate School of Medicine, and colleagues. 8°, cloth, 1091 pp., with 427 illustrations. Philadelphia and London: W. B. Saunders Company, 1946. \$11.00.

This last volume of a standard reference system is the joint work of fourteen members of the faculty of the Graduate School of Medicine of the University of Pennsylvania. To each chapter is appended a selective bibliography. The book is well printed on coated paper, which makes it rather heavy for its size. The complete set of three volumes should be in the reference collections of all medical libraries.

Transactions of the American Association of Genito-Urinary Surgeons. Fifty-sixth annual meeting held at Stockholm, Massachusetts, June 8, 9 and 10, 1944. Volume XXXVII. 8°, paper, 315 pp., with illustrations. Saint Paul and Minneapolis: The Bruce Publishing Company, 1945.

NOTICES

BOSTON MEDICAL HISTORY CLUB

There will be a meeting of the Boston Medical History Club in Sprague Hall at the Boston Medical Library, 8 Fenway, on Monday, January 27, at 8:15 p.m. Dr. Merrill Moore will speak on the subject "Medical Experiences in New Zealand and China."

All interested persons are cordially invited to attend the meeting.

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Tuesday, February 4, at 8:15 p.m. Dr. Ephraim Short, associate professor of medicine, Cornell University Medical College, will speak on the subject "Metabolic Aspects of Renal-Secretion Formation and Prevention."

TUFTS ALPHA OMEGA ALPHA

The Tufts chapter of the Alpha Omega Alpha will meet in the auditorium of the Beth Israel Hospital, Boston, on Wednesday, February 26, at 8:30 p.m. Dr. Harry Gold, of the Department of Pharmacology, Cornell University Medical College, will speak on the subject "Cardiac Therapy."

MASSACHUSETTS MEDICO-LEGAL SOCIETY

The midwinter meeting of the Massachusetts Medico-Legal Society will be held at the Magrath Library, Department of Legal Medicine, Harvard Medical School, on Wednesday, February 12, at 2:30 p.m.

PROGRAM

Short Reports of Cases

Two Cases of Fatal Air Embolism. Drs. Andrew D. Guthrie and Walter W. Jetter.
Rapidly Fatal Unrecognized Intestinal Obstruction due to Adherent Meckel's Diverticulum. Drs. Andrew J. Leddy and Richard Ford.
An Unusual Case of Pentobarbital Poisoning. Dr. George D. Dalton and Russell S. Fisher.
Pseudo-Appendicitis incident to Fatal Reaction to Rabies Vaccine. Drs. Peirce H. Leavitt and Angela Lapi.

Discussion of Problems of Procedure

Circumstances in Which the Filing of an Incomplete "Under Investigation" Death Certificate May Be Desirable. Dr. Timothy Leary.
Reimbursement of Undertakers for Transportation of Bodies and Use of Mortuary Facilities. Dr. Leroy T. Stokes.
When and How Should a Medical Examiner Report a Death for Inquest (Section 8, Chapter 38, General Laws)? Dr. David C. Dow.
Business Meeting.
Refreshments.

CORNELL MEDICAL ALUMNI DAY

Alumni Day for Cornell University Medical College will be held on March 13. It will include registration in the morning, with luncheon at the Nurses Residence, to be followed by the business meeting and a schedule of rounds and conferences in all departments. Dinner will be served at the Hotel Roosevelt, and dancing will conclude the day.

(Notices continued on page xix)

The New England Journal of Medicine

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Volume 236

JANUARY 30, 1947

Number 5

THE ROLE OF LANCEFIELD GROUPS OF BETA-HEMOLYTIC STREPTOCOCCI IN RESPIRATORY INFECTIONS*

THE COMMISSION ON ACUTE RESPIRATORY DISEASES†

IT IS widely recognized that Lancefield Group A streptococci are the causal agents in the majority of streptococcal infections in man. In suppurative or generalized infections the role of other groups of streptococci has been established by the isolation of these organisms in pure culture from collections of pus or from the blood stream. In respiratory infections the problem is more difficult, since various Lancefield groups of beta-hemolytic streptococci are found in the oropharynx of normal subjects. Thus, the isolation of one of these groups from the throat of a patient with respiratory disease does not necessarily establish an etiologic relation. Other methods are therefore required to ascertain the relation of the beta-hemolytic streptococcus to the pathologic process.

Previous reports from this laboratory have emphasized the value of serologic tests in the diagnosis of streptococcal respiratory infections. Studies of a food-borne outbreak showed that at least 85 per cent of patients with known streptococcal disease develop either antistreptolysin or antifibrinolysin during the convalescent period¹ and that these antibodies rarely develop in patients who do not exhibit other evidence of streptococcal infection.²

In serologically proved cases of pharyngitis and tonsillitis caused by beta-hemolytic streptococci, certain clinical, bacteriologic and epidemiologic findings have been of value in specific diagnosis. The clinical characteristics include a history of a sudden onset of sore throat, with associated constitutional symptoms, the physical signs of confluent exudate on the tonsils or pharynx, diffuse

injection and edema of the oropharyngeal mucous membranes and enlargement and tenderness of the cervical lymph nodes.

Laboratory studies usually show a polymorphonuclear leukocytosis in such streptococcal infections. Likewise, single or multiple cultures of the oropharynx ordinarily show large numbers of beta-hemolytic streptococci.³ Not infrequently, however, such clinical and bacteriologic findings are misleading, for many patients, with or without exudative tonsillitis or pharyngitis but harboring beta-hemolytic streptococci in the oropharynx, fail to develop specific antibodies during convalescence.^{3,4}

Finally, certain epidemiologic factors have been found to be of value in determining the role of beta-hemolytic streptococci in respiratory disease. It has sometimes been possible to demonstrate a concentration of cases harboring the same group or type of organism.⁵ Cultural surveys in the normal population and in patients with respiratory disease have been particularly valuable. In one study the total incidence and distribution of groups of beta-hemolytic streptococci were identical in normal soldiers and in patients with respiratory disease who did not develop specific antibodies during convalescence.⁴ It was therefore concluded that the majority of patients harboring beta-hemolytic streptococci and failing to develop antibodies were merely carriers of the organisms who had contracted a respiratory infection caused by other agents.

The present study of 3026 cases of respiratory disease was undertaken to determine the role of various groups of streptococci in ordinary respiratory infections. Many of the patients were found to harbor beta-hemolytic streptococci in the oropharynx. Not only Group A organisms but also streptococci of groups B, C, F, G, H and L were encountered. By the use of bacteriologic, epidemiologic, clinical and serologic methods it was shown that infections were caused by Lancefield groups A, C and G and probably also by groups B and F. The various features of the illnesses produced by the different groups of streptococci are described below.

*From the Respiratory Diseases Commission Laboratory (Regional Station Hospital Section 2, Fort Bragg, North Carolina, now located in the Department of Preventive Medicine, Western Reserve University School of Medicine, Cleveland 6, Ohio).

This investigation was aided by the support of the Commission on Acute Respiratory Diseases, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army, and by grants from the Commonwealth Fund, the W. K. Kellogg Foundation, the John and Mary R. Markle Foundation and the International Health Division of the Rockefeller Foundation to the Board for the Investigation and Control of Influenza and Other Epidemic Diseases for the Commission on Acute Respiratory Diseases.

†Members and professional associates of the Commission on Acute Respiratory Diseases are: Lieutenant Colonel John H. Dungey, M.C., A.U.S., director; Lieutenant Colonel Theodore J. Abernethy, M.C., A.U.S., Major George F. Badger, M.C., A.U.S., Major Norman L. Cressy, M.C., A.U.S., A. E. Feller, M.D., Irving Gordon, M.D., Major Alexander D. Legum, M.C., A.U.S., Charles H. Rammekamp, Jr., M.D., Major Eliot Strauss, M.C., A.U.S., and Captain Hugh Tadlock, M.C., A.U.S.

MATERIALS AND METHODS

Source of Cases

The studies were carried out in the Field Artillery Replacement Training Center at Fort Bragg. The soldiers in this organization arrived in large groups from reception centers located throughout the country. At the time of arrival the majority of the men had been in the Army for less than ten days. For a period of eight to seventeen weeks they received basic training and were then transferred to other stations.

The epidemiologic and clinical features of the respiratory infections occurring in this organization will be described in detail elsewhere.⁵ Briefly, each group of recruits observed during the winter months experienced an epidemic of respiratory infections that resulted in the hospitalization of 15 to 30 per cent of the entire organization.* Although the majority of these illnesses were acute, undifferentiated respiratory diseases,⁵ other infections, such as streptococcal tonsillitis and pharyngitis, nonstreptococcal exudative pharyngitis or tonsillitis, influenza A and B, bacterial pneumonia and primary atypical pneumonia, were encountered. In the present study there were few specific contagious diseases.

Between 1943 and 1945 a total of 3026 patients with respiratory infections admitted to the hospital were studied. This included all patients with respiratory infections entering the hospital from selected organizations of recruits during the winter and spring of 1943-1944 and 1944-1945 and 116 consecutive cases of exudative tonsillitis or pharyngitis observed between April and June, 1943.³ The patients were examined soon after admission, and cultures from the throat were obtained. Usually, a second and a third culture were taken from patients who exhibited exudative tonsillitis or pharyngitis or who harbored beta-hemolytic streptococci in the throat as determined by the first culture. An initial sample of blood was drawn at the time of hospitalization, and in 92 per cent of cases, one or more convalescent specimens were obtained three to eight weeks later.

Carrier Surveys

Throughout most of the period of this study carrier studies were carried out in large samples of recruits who were on active duty. These cultural surveys were made between January and May, 1944 and 1945, during which time most of the patients with respiratory infections were studied.*

Laboratory Procedures

The throat cultures were obtained by the swabbing of both tonsils or tonsillar fossas and the posterior pharynx. The swab was either streaked directly on a blood-agar plate† or placed in 3 to 5 cc of

tryptose phosphate broth, and after thorough mixing, 0.1 cc was transferred to a blood-agar plate. The plates were then incubated at 37°C for twenty-four hours, following which they were examined for colonies showing beta hemolysis under a wide-field binocular microscope. In general, only one colony was picked for grouping and typing, unless two distinct types were recognized. The grouping of the beta-hemolytic streptococci was accomplished by the capillary tube-precipitin method, extracts prepared by Fuller's technic⁶ being used. Commercial serums were available for testing groups A, B, C, D, E, F, G, H and L.

The streptococcal antibodies employed in serologic diagnosis were antistreptolysin and antifibrinolysin. Antistreptolysin O titers were determined by a modification of the method of Hodge and Swift.⁷ The technic used to measure antifibrinolysin has been described elsewhere.⁸ The fibrinolysin employed routinely in this test was prepared from a Group A beta-hemolytic streptococcus (No. 98), in a number of cases, however, determinations were also made with streptococci of groups C and G as the source of fibrinolysin. In both tests for streptococcal antibodies the acute and convalescent specimens of serum were examined at the same time. Under these conditions an increase of titer of either antibody of two or more dilution increments during the convalescent period has been shown to be highly indicative of a specific reaction to the streptococcus.⁹ In the present study, therefore, only changes of this magnitude demonstrated within a period of eight weeks—usually within three weeks—were considered significant.

CULTURAL SURVEYS

The frequency with which the various Lancefield groups of streptococci were found in the oropharynx of normal soldiers and in patients with respiratory infections admitted to the hospital is shown in Table 1. The carrier rates for all beta-hemolytic streptococci in the normal soldiers varied between 8.0 and 9.7 per cent, averaging 8.9 per cent. The rate among patients hospitalized for respiratory disease was 13.9 per cent.

The 5 per cent difference between these rates is largely accounted for by the fact that Group A streptococci were isolated more frequently in the soldiers with respiratory infections than in healthy soldiers. This organism was obtained in the former in 9.5 per cent, and in the latter, in 5.4 per cent—a difference of 4.1 per cent. These data suggest that Group A streptococci were responsible for the majority of the streptococcal infections.

Lancefield groups B, C, F and G were isolated from the oropharynx of both healthy subjects and hospitalized patients, whereas streptococci of groups D, E and H were not found. In the hospitalized soldiers, a Group L streptococcus was isolated from 1 patient at the time of admission. With the excep-

*A soldier with respiratory disease was hospitalized if the oral temperature was over 100°F.

†All blood agar plates contained 0.005 per cent para-aminobenzoic acid.

on of Group A, there were no significant differences in the carrier rates of these various Lancefield groups between the normal soldiers and those hospitalized with respiratory disease. These data indicate that the organisms did not play an important role in the respiratory infections studied. It cannot be concluded, however, that no infections were caused by these streptococci.

SEROLOGIC STUDIES

As pointed out above, the isolation of beta-hemolytic streptococci from the throats of patients with respiratory disease does not necessarily indicate causal relation, and this point is emphasized by the fact that the same organisms were recovered

cultured at weekly intervals. A second specimen of blood was taken three to eight weeks later. Antibody determinations on these sets of serum disclosed that of 236 soldiers who did not harbor beta-hemolytic streptococci, none developed antibodies.² There were 45 subjects who harbored Group A organisms without illness, 1 of whom developed antibodies. In sets of serum collected from 37 soldiers harboring Group C streptococci at some time during the three to eight weeks of study, an increase in the antistreptolysin titer was demonstrated in 1 case. This soldier did not enter the hospital, nor was he seen in the local dispensary. Three of four cultures of the throat taken between the two samples of blood showed Group C streptococci. There was no

TABLE 1 *Comparison of Carrier Rates of Various Lancefield Groups of Beta-Hemolytic Streptococci in 3853 Normal Soldiers and 3026 Hospitalized Soldiers with Respiratory Infections*

ORGANISM	RATES IN NORMAL SOLDIERS				RATES IN HOSPITALIZED SOLDIERS*
	MARCH-MAY 1944	JANUARY 1945	MARCH 1945	1944-1945 COMBINED	1943-1945
	%	%	%	%	%
Group A	5.2	4.6	6.7	5.4	9.5
Group B	—	0.2	0.3	0.1	0.2
Group C	1.0	1.9	1.5	1.4	1.8
Group F	0.1	0.2	0.2	0.2	0.1
Group G	1.6	2.3	0.7	1.6	1.4
Group L	—	—	—	—	0.1
Combination	—	—	—	—	0.1
Not grouped	0.1	0.2	0.3	0.2	0.7
Total carrier rate	8.0	9.4	9.7	8.9	13.9
Number of cultures taken	1585	1229	1039	853	3026

*Admission cultures

from normal soldiers. The number of streptococcal infections occurring in the hospitalized soldiers may be estimated by differences between the carrier rates in the normal and hospitalized soldiers; such studies, however, do not disclose the person who is infected with the organism. It is necessary, therefore, to use other methods to establish the validity of a diagnosis of a streptococcal respiratory infection in the individual patient.

A serologic diagnosis of streptococcal infection was accomplished by the demonstration of an increase in the antistreptolysin or antifibrinolysin titer of the serum obtained during convalescence. Streptolysin O is produced by organisms belonging to Lancefield groups A, C, and G,⁹ and fibrinolysin is produced principally by the same groups, although a few strains of other groups have been observed to cause lysis of fibrin clots.¹⁰ Thus, these two antibody tests are at present considered to be of value only in the diagnosis of infections caused by streptococci of groups A, C and G.

To evaluate the results of the antibody determinations in the hospitalized patients, it was first necessary to establish the frequency with which an increase in titers of antistreptolysin or antifibrinolysin occurred in the normal population. For this purpose a serum specimen was obtained from soldiers on active duty, following which the oropharynx was

significant change in antibody titer in sets of serum collected from 35 soldiers harboring Group G streptococci.

These results demonstrated that in the population studied streptococcal antistreptolysin and antifibrinolysin did not develop in the absence of beta-hemolytic streptococci; moreover, such antibodies were rarely demonstrated in the serum of normal soldiers who harbored these organisms.

Serums taken during the acute and convalescent phases were available for study from 429—92 per cent—of the 465 hospitalized men who harbored beta-hemolytic streptococci in the oropharynx in any of three throat cultures. Of the 429 patients, 161, or 37.4 per cent, developed specific antibodies during the period of convalescence (Table 2). The majority of the increases in antibodies were observed in serums collected from patients harboring Group A streptococci. Of the sets of serum from patients with Group A streptococci alone, approximately half exhibited an increased titer during convalescence, and 39 per cent of patients with Group A in combination with some other group developed antibodies. Of 43 patients with Group C and 41 with Group G streptococci, 16 and 12 per cent, respectively, developed antibodies during the convalescent period. One patient from whom Group L was isolated developed antibodies.

Since the demonstration of an increase of anti-streptolysin or antifibrinolysin titer during early convalescence is a highly specific test² and since such increases were rarely observed in the normal populations studied, it is concluded that the demonstration of a significant increase in these antibodies

TABLE 2 *Antibody Response in Patients with Respiratory Infections Harboring the Beta-Hemolytic Streptococcus*

ORGANISM	NO OF PATIENTS WITH ISOLATION IN ANY OF THREE CULTURES	NO OF PATIENTS TESTED FOR ANTIBODY RESPONSE	ANTIBODY RESPONSE*	
			NO	PER-CENTAGE
Group A	301	283	139	49.1
Group B	6	5	0	
Group C	47	43	7	15.9
Group F	11	11	0	
Group G	44	41	5	12.1
Group H	1	1	0	
Group L	1	1	1	
Not grouped	33	24	2	8.3
Combinations				
Group A and others	19	18	7	38.8
Others	2	2	0	0
Totals	465	429	161	
Average				37.4

*Either antistreptolysin or antifibrinolysin

in the 161 hospitalized soldiers indicated that the respiratory infections were caused by beta-hemolytic streptococci

The frequency distribution of the Lancefield groups of streptococci in the 161 serologically proved cases of endemic streptococcal respiratory infections is presented in Table 3. Group A organisms alone

TABLE 3 *Lancefield Groups of Beta-Hemolytic Streptococci Isolated from Throat Cultures of 161 Patients with Respiratory Disease Who Developed Specific Antibodies During Convalescence*

ORGANISM	TOTAL NO OF PATIENTS	PERCENTAGE OF TOTAL
Group A	139	86
Group A with other groups	7	4
Group C	7	4
Group G	5	3
Not grouped and others	3	2

were isolated from 86 per cent, and Group A alone or in combination with other groups accounted for 90 per cent. The remaining 10 per cent of cases occurred in patients harboring other groups, the largest being Group C with 7 patients, or 4 per cent of this total. Group G was isolated in 3 per cent of the infections.

EPIDEMIOLOGIC, CLINICAL, BACTERIOLOGIC AND IMMUNOLOGIC STUDIES

A detailed study was made of the cases of respiratory disease in which beta-hemolytic streptococci were recovered from the oropharynx. The purpose

of this investigation was not only to establish the relation of the different Lancefield groups to the individual infection but also to describe the response of the host to such infections.

Group A

The difference in the carrier rates of Group A beta-hemolytic streptococci in the normal soldiers and the patients hospitalized for respiratory disease indicated that 124 (41 per cent) of the 3026 cases had been caused by this organism. Serologic studies showed that 139 patients had an infection due to Group A streptococci as determined by the demonstration of an increase in the antistreptolysin or antifibrinolysin titer during convalescence.

The serologically proved infections occurred essentially in a sporadic fashion, only a few small, localized outbreaks caused by a single type of Group A streptococcus were recognized.

Among the 139 patients who harbored Group A streptococci and developed antibodies 101, or 73 per cent, had exudative tonsillitis or pharyngitis. By contrast, the incidence of exudative lesions of the throat in the patients who harbored Group A organisms but failed to develop antibodies was only 34 per cent.

Clinical and laboratory data obtained on patients with exudative tonsillitis and pharyngitis due to Group A streptococci have been presented elsewhere in detail.³ These patients usually complained of soreness of the throat and such constitutional symptoms as feverishness, chilliness, headache and anorexia. Inspection of the throat showed that the exudate was usually discrete to confluent and that the mucous membranes were diffusely injected and somewhat edematous. The regional lymph nodes were likely to be enlarged and tender. The average white-cell count was 16,000, and cultures of the throat showed that Group A streptococci predominated in approximately half the patients. The course of the illness was short, the symptoms usually disappearing by the fourth or fifth day.

The patients who did not have exudative lesions in the throat were seldom thought to have had streptococcal infections when examined at the time of admission. A diagnosis of the specific nature of the illness was possible only after bacteriologic and serologic studies had been completed.

Group B

Six patients were found to harbor Group B streptococci. As expected, an increase in antistreptolysin or antifibrinolysin titer during convalescence was not demonstrated in the serum of the 5 patients tested, since Group B streptococci do not produce streptolysin or fibrinolysin.

There was no evidence of focal concentration of the cases, which occurred sporadically throughout the three-year period. Three of the patients were thought to have undifferentiated acute respiratory

ase⁵ The remaining 3 patients had exudative illitis. In 1 case all three cultures yielded up B streptococci, and in one culture this organism accounted for more than 50 per cent of the ones. The total white-cell count in this patient was 13,600. The second patient had discrete areas of exudate on both tonsils, as well as considerable redness of the soft palate. The lymph nodes were not enlarged or tender. Only one of three cultures yielded Group B streptococci, and the white-cell count was 14,200. The third patient with exudative illitis showed diffuse redness and swelling around

time of admission to the hospital, 6 patients complained of a sore throat. In 3 cases inspection showed areas of discrete exudate on the tonsils. The maximum temperature recorded during hospitalization varied from 99.4 to 103.4°F, and the course of illness was similar to that of a mild streptococcal infection.³ In the majority of cases the temperature became normal within seventy-two hours.

The laboratory studies showed that the average total white-cell count was 10,735. In the 3 patients who had exudative lesions on the tonsils, the total

TABLE 4. *Clinical and Laboratory Data on 7 Patients with Respiratory Disease Who Harbored Group C Streptococci and Developed Streptococcal Antibodies*

CASE NO.	DATE OF HOSPITAL ADMISSION	AGE	SORE THROAT	EXUDATE	MAXIMUM TEMPERATURE	WHITE CELL COUNT	CULTURES FOR GROUP C STREPTOCOCCI			INTERVAL AFTER ADMISSION	ANTI-STREPTOLYSIN TITER	ANTI-FIBRINO-LYSIN TITER
							FIRST	SECOND	THIRD			
					°F					days	units	units
T-101	5/20/43	20	+	+	102	11,400	+	+	0	1 23	50 159	<25 36
T-120	6/1/43	19	+	+	103	11,150	0	0	+	1 39	100 625	56 56
E-292	3/28/44	18	+	0	99.4	8,350	+	++	++	1 24 42	200 317 500	<25 — <25
O-258	1/7/45	24	0	0	103.4	12,200	+	+		1 16 30 51	250 500 500 400	56 56 56 56
O-522	1/23/45	27	+	0	102.2	9,050	+	+		2 17 25	125 250 317	36 56 36
O-581	1/26/45	18	+	+	103	15,600	++	++		1 27 48	200 400 317	<25 <25 <25
O-1070	3/10/45	30	+	0	100.4	7,400	+	0		1 8	125 200	<25 <25

the tonsil, so that a diagnosis of peritonsillitis was made. The regional lymph nodes were enlarged and tender. The white-cell count was only 8,600. A course of penicillin therapy resulted in recovery without abscess formation.

The clinical evidence thus suggested that 3 patients had a respiratory infection caused by the Group B streptococcus. These patients exhibited exudative lesions on the tonsils, 1 developed peritonsillitis, 1 showed enlarged and tender lymph nodes and in 2 the total white-cell count was elevated.

Group C.

The carrier rate for Group C streptococci in the normal and in the hospitalized soldiers was practically identical, being 1.4 and 1.8 per cent respectively. These figures indicated that the majority of the patients were merely carriers and did not have a true streptococcal illness. This was confirmed by the serologic studies, which showed that only 7 hospitalized subjects harboring Group C streptococci developed antibodies during convalescence (Tables 2 and 4).

The illnesses in these 7 patients occurred sporadically throughout the entire period of study. At the

time of admission to the hospital, 6 patients complained of a sore throat. In 3 cases inspection showed areas of discrete exudate on the tonsils. The maximum temperature recorded during hospitalization varied from 99.4 to 103.4°F, and the course of illness was similar to that of a mild streptococcal infection.³ In the majority of cases the temperature became normal within seventy-two hours.

The serums of all 7 patients showed a significant increase in antistreptolysin titer during the convalescent period, but in only 1 subject (Case T-101) did the antifibrinolysin titer increase significantly. Several of the sets of serum (Cases T-101, O-258, O-522, O-581 and O-1070) were tested with fibrinolysin obtained from Group C as well as from Group A streptococci, and no essential difference was observed in the antibody titer. An increase in streptococcal antibodies was demonstrated within twenty-seven days following admission to the hospital in 6 patients. Thus, the clinical and laboratory studies, as well as the bacteriologic and serologic findings, indicated that the majority of the 7 cases presented in Table 4 represented infection by Group C streptococci.

The temperature chart of one of these patients (Case O-581) is presented in Figure 1. This eighteen-

Since the demonstration of an increase of anti-streptolysin or antifibrinolysin titer during early convalescence is a highly specific test² and since such increases were rarely observed in the normal populations studied, it is concluded that the demonstration of a significant increase in these antibodies

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EPIDEMIOLOGIC, CLINICAL, BACTERIOLOGIC AND IMMUNOLOGIC STUDIES

A detailed study was made of the cases of respiratory disease in which beta-hemolytic streptococci were recovered from the oropharynx. The purpose

Group G

The average carrier rate for this group of streptococci was 16 per cent in the normal soldiers and 100 per cent in the patients with respiratory disease. It is thus apparent that few infections were caused by this organism. Serologic tests showed that 5

The temperature chart and the serologic studies of 1 patient (Case O-6) are shown in Figure 3. The onset of this patient's illness was twenty-four hours prior to admission to the hospital, when a sore throat, malaise, chilliness and a slight cough developed. Examination showed diffusely injected and

TABLE 5 Clinical and Laboratory Data on 5 Patients with Respiratory Disease Who Harbored Group G Streptococci and Developed Streptococcal Antibodies

CASE No	DATE OF HOSPITAL ADMISSION	AGE	SORE THROAT	EXUDATE	MAXIMUM TEMPERATURE	WHITE CELL COUNT	CULTURES FOR GROUP G STREPTOCOCCI			INTERVAL AFTER ADMISSION	ANTI-STREPTOLYSIN TITER	ANTI-FIBRINOLYSIN TITER
							FIRST	SECOND	THIRD			
B-8	2/13/44	28	+	0	102	9400	+			Days	Units	Units
										1	125	<25
										10	159	—
										27	200	<25
										32	200	—
E-549	4/23/44	35	0	0	101.8	9200	0	+	0	1	50	<25
										19	200	25
										33	159	—
O-6	10/21/44	27	+	+	103	—	+	+	+	2	125	<25
										25	250	25
										66	400	25
										79	400	25
										95	400	25
O-694	1/31/45	18	+	0	102.4	8650	+			1	63	25
										13	100	36
										24	100	56
										32	83	36
O-971	2/27/45	18	+	0	100.8	570	+	+	0	2	250	125
										32	500	125

patients harboring Group G streptococci developed antibodies during convalescence. A summary of the data in these cases is presented in Tables 2 and 5. All but 1 of the patients complained of a mild sore throat at the time of the first interview, and in

swollen tonsils on which areas of discrete exudate were present. The cervical lymph nodes were small and not especially tender. Cultures on three successive days showed Group G streptococci. The antistreptolysin titer on admission was 125, and on the twenty-fifth day was 250. Antifibrinolysin determinations were made with the use of both Group A and Group G streptococci as the source of fibrinolysin. The titer with both fibrinolysins, which had been less than 25 units on the initial serum specimen, had increased to only 25 units on the twenty-fifth day.

Case O-694 is of interest since the increase in antistreptolysin titer was demonstrated on the thirteenth day of illness. The titer of serum specimens obtained twelve and nine days before admission was 63 units of antistreptolysin. Also, cultures of the throat obtained thirteen, twelve and one days prior to admission showed Group G streptococci. It therefore appears that the increase in antistreptolysin titer was due to this organism. No increase in titer to fibrinolysins of groups G, C and A was demonstrated in the serums obtained from this patient.

The first two cultures in Case O-971 showed Group G streptococci, and the antistreptolysin titer increased from 250 to 500 units in thirty days. Previous specimens of blood obtained fifteen and fifty-seven days prior to admission to the hospital showed a titer of 250 units. There was no change in the antifibrinolysin titer when tested by fibrino-

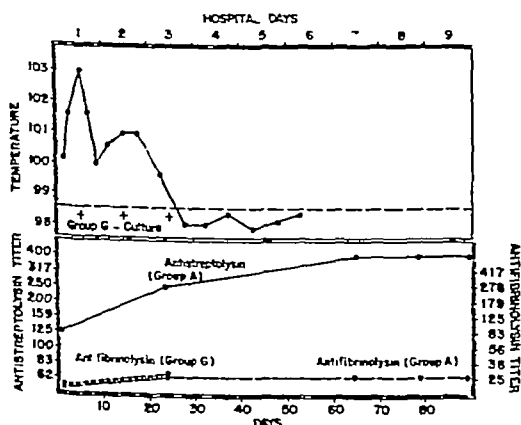


FIGURE 3 Clinical Chart of a Patient with a Group G Streptococcus Infection.

In 1 case exudate was present on the tonsils. The maximum oral temperatures observed during the course of these illnesses varied from 100.8 to 103°F. The temperature became normal within two days in 4 cases, and in 1 it reached a normal level within three days.

year-old soldier developed a nonproductive cough and mild coryza a week prior to admission to the hospital. Five days later he noticed a sore throat, as well as slight chilliness without a true rigor

coccal illness. Seven patients* were found to have exudative tonsillitis or pharyngitis. The temperature curves, throat cultures and white-cell count are presented in Figure 2. Three patients (Cases

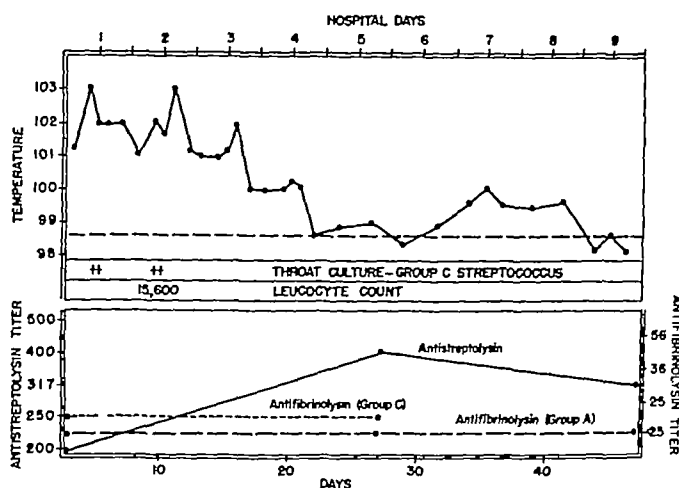


FIGURE 1 Clinical Chart of a Patient with a Group C Streptococcus Infection

Inspection of the throat showed that the tonsils and surrounding tissues were diffusely injected, with areas of discrete exudate on both tonsils. The cervical lymph nodes were large and tender. The white-cell count on the second hospital day was 15,600, with 69 per cent neutrophils. The antistreptolysin titer increased from 200 to 400 units in twenty-six days, but no increase in antifibrinolysin was demonstrated in tests made from either Group A or Group C streptococci.

Group F

Eleven patients with respiratory illnesses were found to harbor Group F streptococci in the throat, and all these patients entered the hospital in March and April, 1944, when 857 patients admitted to the hospital were studied; there was no other evidence that these cases occurred in an epidemic fashion, since all the soldiers were housed in different barracks. A survey of the carrier rate for beta-hemolytic streptococci made during the same period showed Group F organisms in only 2, or 0.12 per cent, of 1568 soldiers on active duty. On the basis of the first hospital culture, 3, or 0.35 per cent, of 857 patients harbored the organism.

In the hospital 6 patients were housed in one ward, and 4 in another. This suggested the possibility of cross infection in the hospital; examination of the dates of admission and discharge, however, revealed that cross infections were unlikely in the majority of cases.

There was some clinical evidence that a few of the patients with Group F streptococci had a strepto-

coccal illness. Seven patients* were found to have exudative tonsillitis or pharyngitis. Several showed a rather brisk febrile response.

In only 2 patients were Group F streptococci isolated in all three cultures; in 3 others, two cul-

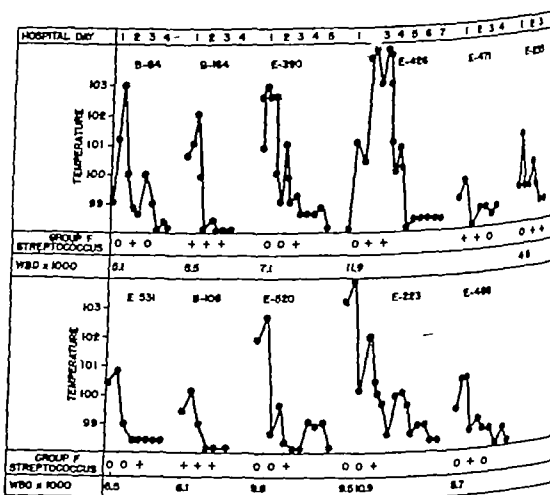


FIGURE 2 Temperature Charts of Eleven Patients with Respiratory Infections Who Harbored Group F Streptococci in the Oropharynx

tures showed this organism. The white-cell count was slightly elevated in only 2 patients (Cases E-426 and E-223).

*Cases B-84, B-164, E-390, E-426, E-471, E-223 and E-531

tain selected organizations of recruits but also surveys among the healthy soldiers in the same organizations. Thus, the differences in the prevalence of beta-hemolytic streptococci among the healthy soldiers and those hospitalized with respiratory disease should indicate the group or groups responsible for the illnesses. The carrier rate for all beta-hemolytic streptococci in the healthy soldiers was about 9 per cent, whereas 14 per cent of the hospitalized soldiers carried these organisms. The difference in rates was due almost entirely to Group A streptococci.

By the additional use of serologic, clinical and epidemiologic data, segregation of the specific patients with respiratory illness due to the beta-hemolytic streptococcus was possible. That such a method was valid was shown in a previous study⁴ and again by the data presented above. If all the hospitalized patients who developed either antistreptolysin or antifibrinolysin during convalescence were excluded from the cultural surveys, the carrier rates in the healthy and hospitalized soldiers were approximately the same. This indicates that the beta-hemolytic streptococci in the oropharynx of the majority of the patients with respiratory illness who did not develop antibodies were not causally related to the infectious process.

On the basis of the demonstration of antibody formation during the convalescent period, 38 per cent of all cases of respiratory disease that showed beta-hemolytic streptococci were cases of streptococcal infection. At this Army hospital, beta-hemolytic streptococci were recovered from 465 of 126 patients with respiratory infections. Thus, serologically proved cases of streptococcal disease accounted for approximately 6 per cent of the respiratory admissions in recruits over a three-year period. It is to be emphasized, however, that during this period there were no large epidemics and that the majority of streptococcal illnesses occurred sporadically.

The serologic reactions observed in the serums collected from these patients harboring different Lancefield groups of beta-hemolytic streptococci were of considerable interest. Streptolysin O is known to be produced only by organisms belonging to groups A, C and G.⁹ It is well established that Group A infections are followed by an increase in the antistreptolysin titer in the majority of cases. Antibody studies have rarely been employed in the analysis of infections caused by other groups. Kirby and Rantz¹⁴ described an increase in antistreptolysin in the serum of a patient with bacteremia due to a Group C streptococcus. In the present study 7 patients harboring this organism and 5 with Group G streptococci developed antistreptolysin during convalescence. Longcope¹⁵ studied a thirteen-year-old boy with an infection due to the Group F streptococcus whose serum exhibited an increase in antistreptolysin titer. No case of a rise in these anti-

bodies, however, was observed in the 11 patients harboring Group F strains reported above.

The antifibrinolysin response to infection by streptococci belonging to Group A have been described elsewhere.¹⁶ In that study a correlation was demonstrated between the ability of the homologous strain to produce fibrinolysin *in vitro* and the occurrence of an antifibrinolysin response following infection. In the present study 1 of the 7 patients with infections due to Group C organisms and none with infections due to those of Group G exhibited a significant increase in the antifibrinolysin titer. This low incidence of antifibrinolytic response was expected, since both organisms usually produce less fibrinolysin than Group A.¹⁰ The median *in vitro* production of 452 Group A strains was 117 units, of 137 Group C strains, 61 units, and of 104 Group G strains, 20 units of fibrinolysin.

In several of the patients with infections due to groups C and G the serums in the acute and convalescent phases were tested with fibrinolysin made from Group A, Group C and Group G streptococci. With the use of quantitative methods,⁸ no significant differences in the titers of antifibrinolysin were demonstrated with these three preparations. These results, as well as those of a more detailed study,¹⁷ show that fibrinolysins produced by beta-hemolytic streptococci of groups A, C and G are immunologically identical. Kirby and Rantz¹⁴ found that the antifibrinolysin titer following an infection with Group C was approximately the same when measured by either Group A or Group C fibrinolysin. They suggested that, from a qualitative standpoint, these fibrinolysins are similar.

On the basis of serologic tests, 90 per cent of the streptococcal illnesses were due to Group A, 4 per cent to Group C and 3 per cent to Group G. A detailed study of the infections caused by streptococci of groups A, C and G failed to show any outstanding differences in the clinical pattern. The illnesses produced by each group were mild and of short duration. A few of the infections included as cases of infection with Group C or G may have been due to Group A, since in some the number of cultures obtained were not adequate to rule out the presence of the latter organism.

The role of beta-hemolytic streptococci of groups B, F, H and L in the respiratory illnesses could not definitely be ascertained. There was some clinical evidence that groups B and F occasionally produce an infection, since several patients exhibited such clinical features as a discrete exudate over the tonsils, diffuse redness and edema of the soft palate, tonsils and pharyngeal mucosa and enlargement and tenderness of the cervical lymph nodes.

SUMMARY

A study undertaken to show the importance of the Lancefield groups of beta-hemolytic streptococci in mild respiratory infection is reported. In a large

lysins prepared from Group A, Group C and Group G streptococci

In Case E-549 only one culture was positive for Group G streptococci, but the antistreptolysin titer increased within nineteen days after admission to the hospital. Case B-8 also had only one culture that showed a Group G streptococcus. This patient entered the hospital because of weakness, chilliness and feverishness of two days' duration. The only respiratory symptoms were sneezing, coryza and a slight cough. Seven days after entry, the patient was discharged from the hospital, only to return two days later, when a blood specimen showed that the antistreptolysin titer had increased from 125 to 159 units. Cultures of the throat and sputum again showed Group G streptococci. A throat culture taken twelve days after the first admission showed a Group A, nontypable streptococcus. It seems probable, although not definite, that the illness in this patient was due to Group G, since an antibody response had occurred prior to the isolation of the Group A organism.

Thus, 5 of the 41 patients with respiratory disease who harbored Group G streptococci in the oropharynx exhibited serologic evidence of a streptococcal infection (Table 5). It is of some interest that only 1 of these patients had exudative tonsillitis. The white-cell count was not elevated in the 4 patients examined.

Group H

The patient who harbored Group H streptococci showed the organisms in only one of three cultures. This patient had exudative tonsillitis and pharyngitis. There was little injection around the areas of exudate, however, and the cervical lymph nodes were not enlarged or tender. The white-cell count was 5500.

Group L

The patient who harbored Group L streptococci in the throat and developed antibodies during convalescence entered the hospital because of feverishness, cough, hoarseness and nasal discharge. He appeared only mildly ill, and the oral temperature was 101°F. The soft palate was slightly edematous but not injected. The tonsils had been removed. The pharynx showed only slight redness, and the cervical lymph nodes were neither enlarged nor tender. Fine rales were heard over the right lower posterior portion of the chest, and a roentgenogram showed a small area of pneumonia above the right diaphragm. The white-cell count was 15,800. The only throat culture obtained was at the time of admission, Group L streptococci were identified. After two days in the hospital the temperature became normal, and the pulmonary infiltration disappeared by the sixteenth day. The clinical diagnosis was primary atypical pneumonia.

The antistreptolysin titer measured 200 units on admission, 250 units on the fourteenth day and 317 units on the twenty-ninth day. The antifibrinolysin titer, which on admission was 100 units, was 200 units fourteen and twenty-nine days later. Since there is no information whether Group L streptococci produce streptolysin or fibrinolysin, and since adequate cultures were not obtained to rule out the presence of some other group, it was impossible to determine if this illness was due to Group-L streptococci.

DISCUSSION

With the exception of scarlet fever and puerperal infection, information concerning the importance of the different Lancefield groups of beta-hemolytic streptococci in various types of infections is meager. Scarlet fever is rarely caused by streptococci of groups other than Group A. Hare,¹¹ in a summary of several investigations, reported that 115 patients with scarlet fever showed Group A streptococci and that in 2 cases the grouping was unknown. Gardner¹² isolated a Group G and a Group F streptococcus respectively from 2 of 21 patients with the disease.

Apparently beta-hemolytic streptococci of groups other than Group A are frequent causative agents in puerperal fever and septic abortions. In Hare's¹¹ summary of 206 patients with these infections, 3 cases were caused by Group B, 3 by Group C and 1 each by groups D and G and ungrouped organisms, the remainder being associated with Group A streptococci. Hill and Butler¹³ reported 110 cases of beta-hemolytic streptococcus infection of the uterus, 82 of which were caused by Group A, 12 by Group B, 10 by Group C and 6 by Group G. Thus, approximately 25 per cent of these patients had infections caused by beta-hemolytic streptococci not belonging to Group A.

In erysipelas there is some indication that Group C plays a significant role, since in 28 cases studied, this organism was isolated in 5 cases.¹⁴

Further data indicating the importance of streptococci of groups other than Group A are obtainable only from isolated case reports and cultural surveys of hospitalized patients. The report of one or several cases—or even of an occasional epidemic—due to the rarer groups of beta-hemolytic streptococci is of little aid in the estimation of the frequency with which the various groups cause disease. Likewise, reliable data are difficult to obtain from reports on cultures obtained from hospitalized patients with various types of infections, since the isolation of one of the groups of streptococci, especially from the oropharynx, does not necessarily indicate a causal relation to the pathologic process.

In the present study several sources of information were used to determine the role of the groups of beta-hemolytic streptococci in respiratory infections. These included not only cultures of all patients with respiratory infections admitted to the hospital from

extremely narrow, it is easy to maneuver, and there is less danger of destroying surrounding structures

The usual type of Achilles shortening found in my patients may be attributed in the main to lists applied to the lower extremity with the foot in some degree of plantar flexion. Also, following compound comminuted fractures, even though the foot has been encased in plaster in a neutral position, the tendon or belly of the gastrocnemius muscle becomes scarified and tends to contract, with subsequent shortening. Occasionally, after peroneal lacerations, patients fail to wear dropped-foot or night

The operative procedure is illustrated in Figure 2. The lower extremity is properly draped. A blood-pressure cuff may be applied about the midhigh level and inflated to a pressure equivalent to 600 mm of mercury, but its use is optional. The plantar surface of the foot is then placed against the abdomen of the operator, so that the Achilles tendon is stretched. Thus, both hands of the surgeon are free to carry out the procedure, and at the same time, tension of the tendon is maintained. With the use of the fingers of one hand to estimate the approximate width of the tendon, a stab wound on

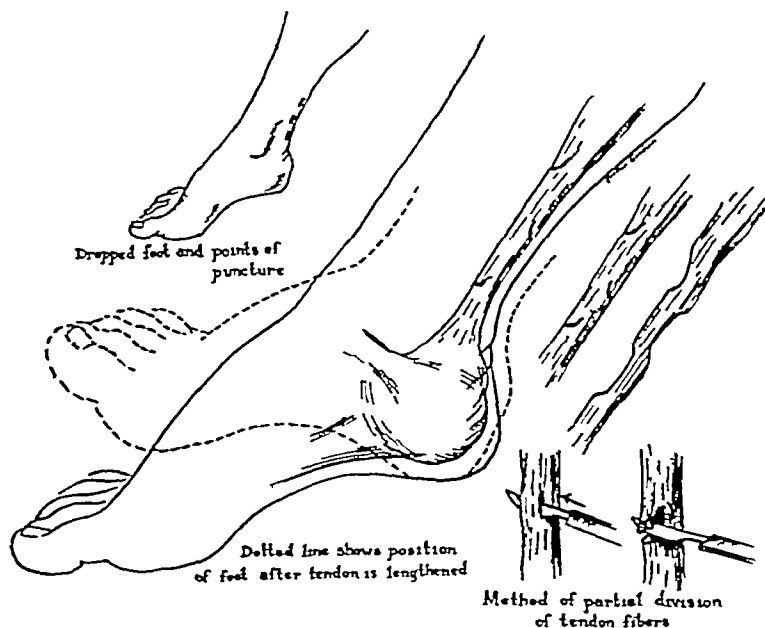


FIGURE 2 Diagrammatic Representation of the Operative Procedure in Triple Hemisection of the Achilles Tendon

splints, with the result that a shortened tendon often develops. These conditions are opposed to the usual civilian type of postpoliomyelitis in which muscle imbalance results in shortening of the Achilles tendon.

White has described one of the main problems in elongating the Achilles tendon as follows: "The explanation of the difficulty encountered in lengthening the heel cord by simple subcutaneous tenotomies lies in the fact that there is approximately a ninety-degree twist of the structure on its own axis within the surgical field, and that when even two thirds of the medial fibers have been severed at one level and two thirds of the lateral fibers at another level, enough fibers miss being cut to cause the tendon to 'hang'." This statement describes the tendinous arrangement most adequately. This anatomical fact regarding the tendon of the gastrocnemius muscle is not, however, well known and bears repetition.

the medial aspect of the extremity is made into the substance of the tendon about 2.5 cm superior to its insertion into the calcaneal tuberosity, with the flat of the knife blade on the same plane as the longitudinal fibers of the tendon. Greater success is assured if, when the tip of the blade has pierced the tendon, its course is altered from a simple transverse to a posterolateral direction. Because of the twist in the Achilles tendon, as demonstrated by White, at least a third of the tendon at this level must be divided. Caution must be taken to follow the medial approach, which alone gives assurance that the posterior tibial nerve or vessels will not be injured. This point cannot be too strongly emphasized.

Once the operator is certain that the point of the blade has passed through to the lateral aspect of the tendon, the knife is turned through an arc of 90° in an anterior direction. Provided that this maneuver

Army camp, only 6 per cent of cases among patients admitted to the hospital from an organization of new recruits were due to streptococcal infections. Bacteriologic and immunologic studies demonstrated that 90 per cent of the infections were due to Group A, 4 per cent to Group C and 3 per cent to Group G. Clinical and epidemiologic evidence suggested that a few patients had infections due to groups B and F.

The illnesses produced by the various groups of beta-hemolytic streptococci were similar. Streptolysin O antibodies were demonstrated in serum specimens obtained from patients harboring organisms of groups A, C and G. Antifibrinolysin developed in patients with infections due to Group A and Group C streptococci. The titer of antifibrinolysin in the serum specimens taken during the acute and convalescent phases from patients with infections due to groups C and G was identical when measured with fibrinolysin prepared from organisms of groups A, C and G.

REFERENCES

- 1 Commission on Acute Respiratory Diseases. Study of food-borne epidemic of tonsillitis and pharyngitis due to beta hemolytic streptococcus type 5. *Bull Johns Hopkins Hosp* 77:143-210, 1945
- 2 *Idem*. Studies of streptococcal fibrinolysis. IV. Clinical application of quantitative antifibrinolysin test. *J Clin Investigation* 25:352-359, 1946
- 3 *Idem*. Endemic exudative pharyngitis and tonsillitis: etiology and clinical characteristics. *J A M A* 125:1163-1169, 1944.
- 4 *Idem*. Role of beta hemolytic streptococci in common respiratory diseases. *Am J Pub Health* 35:675-682, 1945
- 5 *Idem*. Unpublished data
- 6 Fuller, A. T. Formamide method for extraction of polysaccharide from haemolytic streptococci. *Brit J Exper Path* 19:150-159, 1938
- 7 Hodge, B. E., and Swift, H. F. Varying hemolytic and contact combining capacity of streptolysins, influence on testing for A-B streptolysins. *J Exper Med* 58:277-287, 1933
- 8 Kaplan, M. H., in collaboration with Commission on Acute Respiratory Diseases. Studies of streptococcal fibrinolysis. III. Quantitative method for estimation of serum antifibrinolysin. *J Clin Investigation* 25:347-351, 1946
- 9 Todd, E. W. Comparative serological study of streptolysins derived from human and from animal infections with notes on peristreptococcal haemolysin, tetanolysin and staphylococcus toxin. *J Path & Bact* 39:299-321, 1934
- 10 Commission on Acute Respiratory Diseases. Unpublished data
- 11 Hare, R. Puerperal sepsis and its prevention. *Canad. Pub Health* 28:554-563, 1937
- 12 Gardner, H. M. Occurrence of different groups of haemolytic streptococci in human infections. *Edinburgh M J* 46:648-654, 1939
- 13 Hill, A. M., and Butler, H. M. Haemolytic streptococcal infections following childbirth and abortion: clinical features, with special reference to infections due to streptococci of groups other than A. *M J Australia* 1:293-299, 1940
- 14 Kirby, W. M. M., and Rantz, L. A. Streptococcal bacteremia cured with sulfadiazine: report of case of infection caused by hemolytic streptococci of Lancefield group C with review of literature and presentation of immunologic data. *Arch. Int. Med.* 71:620-623, 1943
- 15 Longcope, W. T. Studies in variations in antistreptolysin titer of blood serum from patients with hemorrhagic nephritis. II. Observations on patients suffering from streptococcal infection, rheumatic fever and acute and chronic hemorrhagic nephritis. *J Clin Investigation* 15:277-294, 1936
- 16 Commission on Acute Respiratory Diseases and Kaplan, M. H. Quantitative study of fibrinolysin antifibrinolysin reactions. *Science* 101:120-122, 1945
- 17 Kaplan, M. H., and Commission on Acute Respiratory Diseases. Immunologic similarity of streptococcal antifibrinolysin. *Proc. Soc. Exper Biol & Med* 63:50-53, 1946

TRIPLE HEMISECTION: A SIMPLIFIED PROCEDURE FOR LENGTHENING THE ACHILLES TENDON*

LIEUTENANT COLONEL RAFE NELSON HATT, M.C., A.U.S., AND MAJOR TIMOTHY A. LAMPHIER, M.C., A.U.S.

ABOUT twenty years ago, a new procedure for lengthening the Achilles tendon was first employed. It is known as triple hemisection. Dr. Michael Hoke, who is believed to have been the first to use this simplified technic, did not publish his results. And yet, according to White,[†] "lengthening the heel cord is the commonest single operative procedure in the repertoire of most orthopedic surgeons, and the reporting of any simplification of the technique seems justified."

Our purpose in describing this operation is to re-emphasize its simplicity. Excellent results have been obtained without the necessity of using the so-called "open tenoplasty technic." Certainly, the much shorter operative time alone indicates triple hemisection of the Achilles tendon as the procedure of choice. Surgical exposure of a large portion of a tendon or of any internal structure necessarily carries with it the possibility of postoperative sepsis. Even the availability of such new drugs as penicillin and

streptomycin does not mean that infection of tendon sheaths is easy to control. Another and even more important consideration is that the continuity of the tendon is maintained.

A so-called "tenotome" (Fig. 1), is used in this procedure. Its outstanding feature is a narrow thin blade that requires only a minute puncture hole in



FIGURE 1 Photograph of Tenotome

the skin prior to piercing the substance of the tendon. Once the knife has been inserted into a tendinous structure, there is no danger that the blade will be separated from the handle. Since the blade

*From the Cushing General Hospital, Framingham, Massachusetts.
[†]White, J. W. Torsion of Achilles tendon: its surgical significance. *Arch. Surg.* 46:784-787, 1943.

lengthening and thus to correct the greater degree plantar flexion

One criticism of this technic is that the ruptured bers tend to become adherent to surrounding ructures. This has not happened, however, in the undreds of lengthening procedures carried out as escribed above. Certainly, the open tenoplastic

procedure traumatizes and exposes a greater amount of subcutaneous structures than the simpler triple hemisection. One of us (R N H) has had the opportunity to use this technic frequently during the past twenty years. The results obtained have been excellent and confirm the value of this simple method

PRURITUS ANI*

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A REVIEW of the voluminous literature on the subject of anal pruritus reveals that nearly as many theories regarding the etiology of this condition have been advanced and methods of treatment advocated as there have been authors. Several conclusions might be taken from this. First, the final answer has not been written, and there may be several etiologic factors involved in many of the patients with this condition. Secondly, because so many preliminary good results have been reported following so many apparently different types of therapy directed primarily toward the perianal region, the treatment of the patient, in addition to the management of the local anorectal condition, may be an important factor. Thirdly, there may be a factor common to many of these apparently different types of treatment that has been overlooked by the attention given the variety of drugs, injections and surgical procedures used on the perianal area.

The fact that many of these methods are not permanently successful is apparent in that a large number of the patients seen at the Lahey Clinic have already had some type of local anorectal therapy for anal pruritus without more than temporary relief.

It is not the purpose of this paper to announce that a cure for every patient with anal pruritus has been discovered or to present a long statistical study, but it is a condition that is often seen and one in which we have been particularly interested for several years. Many of the studies reported in the literature have not been carried out, and there are many types of treatment that we have not utilized, it is a frequent complaint, however, and many of the intractable cases present serious and complicated problems.

As a result of this experience we have developed certain theories regarding the etiology of this condition and methods of treatment. It is the purpose

of this presentation to discuss the factors that may give rise to anal itching or may cause an anal pruritus to become an intractable and definite pathologic entity, and to present the methods of treatment that have proved most satisfactory.

ETIOLOGY

Some precipitating factor begins an anal pruritus. An anal itching is often noticed following a period of diarrhea or constipation, particularly if there is some associated anorectal disease. It is also a frequent observation that fatigue, worry and nervous tension are associated. Usually, this itching is transient and causes only mild and temporary discomfort.

The natural tendency for relief of an anal itch is to rub or scratch, which, if continued, causes local congestion, trauma and irritation and allows the introduction of infection into the perianal skin and adjacent tissues. This, in turn, causes more itching and sufficient excuse for further scratching and irritation of the part. Thus, a cycle of scratching and itching is established that, in the long-standing, intractable case, may develop into such a habit fixation that the patient is powerless to let himself alone and is awakened from a sound sleep, scratching himself.

This scratch-itch syndrome is a basic factor in the background of a large number of patients with an intractable anal pruritus and must be thoroughly appreciated by both the physician and the patient. Patients with an intractable condition of this type who have been treated by several physicians with various remedies often state that no one had ever taken the time to emphasize the importance of the avoidance of irritation to the parts affected. It is my belief that many of the intractable cases would never have developed if this single principle had been followed in the early stages of the disease.

Scratching is not the only cause of pruritus ani—it is an important factor, particularly in intractable cases, but it must not be overlooked that something additional caused the original itch. In

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has been carried out properly, approximately one third of the tendon will have been divided.

When a second operative site, about 2.5 cm above the original stab wound, has been selected, the tenotome blade is again passed by a medial approach through the skin and into the substance of the tendon. The course of the blade is again altered from a simple transverse to a slightly antero-lateral direction. After the operator has determined that the tip of the blade is felt subcutaneously on the lateral aspect of the extremity, the blade is rotated through an angle of 90° posteriorly, and again approximately one third of the structure will have been divided.

The third — or most proximal — puncture wound is made about 2.5 cm above that just described, the tenotome blade passing through the substance of the tendon in a posterotransverse direction. Again, the blade is turned through an angle of 90° anteriorly, and the operator is conscious that the fibers have been divided.

The next maneuver consists in the exertion of greater pressure against the plantar surface of the foot opposite the metatarsal heads. The weakened tendon, which relaxes as the fibers slide apart, can be lengthened until the foot is dorsiflexed to an angle greater than 90° . One should not be too enthusiastic in obtaining a markedly acute angle in dorsiflexing the foot, since the tendon may be completely divided and its continuity lost.

The entire procedure can be completed within a few minutes by an experienced operator. The assurance that the continuity of the tendon has been maintained is of primary concern. The results obtained by this simple method leave open to doubt the desirability of other, more prolonged procedures.

After the dorsiflexion of the foot to the desired angle, the three puncture wounds are dressed with sterile gauze. Sutures are entirely unnecessary, for the wounds are so small that the skin edges do not require approximation. With the foot maintained in the dorsiflexed position at all times and with the leg fully extended to 180° at the knee joint, the extremity is encased in plaster from the toes to the lower thigh level. Jack-knifing of the extremity at the knee joint while the cast is being applied must be avoided, to maintain tension on the Achilles.

An inexperienced operator may completely bisect the tendon, and when this occurs, a modified open tenoplastic repair must be resorted to.

Postoperatively, the cast is not removed in less than four weeks, to prevent recurrent shortening of the tendon. From the fifth through the eighth week the patient is allowed to remain ambulatory during the day, but a posterior plaster shell or a so-called "night ladder splint" should be worn while the patient is sleeping.

The double-exposure photographs (Fig. 3) represent the degrees of dorsiflexion before and four weeks after operation. Shortening of the Achilles tendon

in this case resulted because the patient had previously had a cross-leg skin flap applied to his heel and the foot had been left in a flexed plantar position for several weeks.

* * *

The triple hemisection method of Dr. Michal Hoke for lengthening the Achilles tendon has been described in detail. Difficulties arise in attempting



FIGURE 3 Double-Exposure Photographs Showing the Degree of Dorsiflexion before (upper) and after (lower) Operation.

the procedure in cases in which unsuccessful subcutaneous tenotomy has been attempted at some previous date. Occasionally, inexperienced operators attempt to gain too great an angle of dorsiflexion and completely disrupt the tendon. It should be remembered that, in marked deformities, the puncture wounds of the heel cord should be proportionately separated farther apart to obtain greater

combat zone. The majority of these men, experienced infantrymen, had the highest morale and were too busy and occupied most of the time to develop an anal fixation and spend their time worrying and itching and scratching. It must be remembered that these men were frequently without baths or clean clothes for days at a time and were in a hot, humid climate.

Mechanical Factors

Nearly every case of anal pruritus is precipitated by some local mechanical factor. If this itching begins when certain other favorable factors exist and relief is not obtained, the condition may become intractable.

Minor trauma to this area is not unusual. The act of defecation may cause an abrasion or a fissure. The effects of instrumentation, rubbing or scratching may begin an itch. Hemorrhoids may be responsible, but probably less frequently than has been believed. Large skin tags, however, by rubbing together, causing congestion and interfering with mechanical cleanliness of the area, often seem to be important.

A contracted anal ring, a condition referred to in the literature as pectenosis, is a frequent factor. Infected or inflamed crypts are rarely involved, in our experience.

TREATMENT

A general physical examination, including an anoscopic and proctoscopic examination of the lower bowel, should be done in all cases. Routine blood counts and a urine examination should be carried out. In the majority of cases, after examination, the cause will be obvious, and the treatment apparent. In many, however, further laboratory and roentgenologic studies will be required and possibly the help of the dermatologist, internist, gastroenterologist or psychiatrist. It is to be noted that the original or precipitating factor in the long-standing case of anal pruritus may have disappeared and, from the standpoint of therapy, may not be particularly significant.

For constitutional treatment, the most important requirements are adequate rest, relaxation and relief from tension. Hospitalization and temporary but adequate sedation may be necessary in severe cases. A small amount of a combination of a tincture of belladonna and luminal, particularly when there is an associated spastic colon, is a helpful sedative. Chloral hydrate ensures a good night's sleep. A normal bowel function should be established as early as possible, and the intake of carbohydrate, excess roughage and alcohol should probably be reduced.

Excessive sweating, which may be troublesome, is the only indication for radiation therapy, since in our experience cases in which such therapy was used routinely nearly all recurred after a period of six

to eight months of temporary relief, and it was found that they were invariably much more difficult to control. We have observed cases in which cancer developed in the anal area from the excessive use of radiation therapy. At the present time it is rarely used.

The presence of seborrhea, psoriasis, eczema, contact dermatitis and certain other strictly dermatologic conditions should not be overlooked. Special studies, particularly for food allergies, may be necessary in certain stubborn cases.

In considering local therapy, we are in entire agreement with Stokes that too much attention has been given to this phase of the management of the patient with anal pruritus. Most patients with long-standing intractable anal pruritus have had one or more series of radiation treatments, undercutting operations or alcohol injections, hemorrhoidectomy, cryptectomy, rectal dilatation or some other surgical procedure. They present a scarred anal ring and perianal area that has obviously been made worse by such treatment. Many of these patients had never been instructed to keep themselves clean and stop scratching.

Several years ago, while doing an alcohol injection on a patient with anal pruritus, I found a visitor very much interested in the procedure and in the disease. She was a missionary who had been in charge of a hospital in India for many years and had never seen a native with an anal pruritus of the type described in the literature, the explanation, in her opinion, being the fact that the Indians had never known modern toilet tissue and merely washed themselves frequently. Certainly, adequate local hygiene is the basis of any local therapy for anal pruritus. That this is not the only factor, however, was borne out by my experience in the Army referred to above.

Our patients are routinely advised to wash themselves often with cotton moistened in warm water and to eliminate toilet tissue and soap. They are instructed never to touch themselves with their fingers or any object other than cotton. The ensuing dryness and cleanliness and the avoidance of trauma will indefinitely control many of the mild cases of anal pruritus.

Among the local medications, potassium permanganate, in a strength of 65 mg to 1 liter of hot water, is used almost routinely. Patients with a mild pruritus are instructed to sit in a basin of this solution for fifteen to twenty minutes at a time as often as is necessary to control the itching. The usual cause of failure in the use of potassium permanganate has been that the solution has not been employed for a sufficient period. The application of a 1 per cent solution of phenol in calamine lotion may be all that is necessary to relieve the difficulty. In the severer cases, continuous wet dressings and hospitalization may be required. Burow's solution, containing 1 per cent alum and

intractable cases this precipitating factor may have disappeared or become so altered by the passage of time and the development of local perianal changes that it is no longer significant, but it must be remembered that at one time there were factors favorable for the development of an itch in this region. It must also be recognized that the incidence of recurrence in this disease is high following alcohol injections, undercutting operations and other procedures in which a definite cessation of itching and relief from the tendency to scratch have been established, indicating that there are other underlying factors than the mere scratch-itch syndrome.

A wide range of factors may be responsible for the development of anal pruritus, and in long-standing intractable cases many factors may be involved in a single patient. Stokes¹ has divided into five groups the factors that should be considered in establishing the etiology of a given case of anal pruritus. These are considered below.

Physiologic Factors

The anorectal region contains a sweat apparatus called the apocrine system, which, similar to the axillary, submammary and periumbilical areas, is a part of the sexual glandular system and has, among others, two important characteristics: the sweat contains protein and excess carbohydrate and is more alkaline than ordinary sweat, and the apocrine sweat glands are peculiarly responsive to emotion, particularly sexual tension. This area, with its high-protein and high-carbohydrate content and alkalinity, is thus an ideal medium for the introduction of fungous infections and secondary invaders.

The physiologic state of the gastrointestinal tract itself may be important. It is not unusual to find that a stubborn constipation or diarrhea — owing to an atonic or spastic bowel — aggravates an anal pruritus.

There has been considerable discussion on the effect of intestinal flora on this condition. We have had little experience with studies of the intestinal flora and, in general, have not been impressed with the importance of this factor. We have had no experience with the use of autogenous vaccines. It has seemed sufficient to establish a normal bowel function, and adequate treatment of an irritable colon has been of value in the treatment of many stubborn cases.

It has been noted that many soaps are irritating in this condition. In patients who have a deficient amount of fat in their normal skin secretion, the excessive use of soap often causes local irritation. The sodium salts of saturated fatty acids are relatively irritating, and the sulfite in certain toilet tissues has been reported as a frequent source of irritation.

Excessive carbohydrate intake not only predisposes to an increased alkalinity of the part affected

but also causes an increased hydration of the skin. Excessive fruit juices may have the same effect. Alcohol, as a peripheral dilator, may be significant.

Infective Factors

The role of fungous infections in anal pruritus has received considerable attention.² Terrell and Shaw³ reported an incidence as high as 60 per cent in cultures taken from the perianal area. In the few patients in our series on whom careful bacteriologic studies were made, the incidence of fungous infections was not high. Pyogenic flora, with occasional hemolytic streptococci, were the usual findings. Stokes¹ has pointed out that a variety of organisms may be associated with the disease, many of which, generally considered nonpathogenic, seem to become pathogenic for the patient concerned.

Allergic Factors

An allergic background has been encountered in a few of our patients with anal pruritus. Frequently, however, the exact relation of the anal itching is difficult to evaluate. Certain patients exhibit an apparent susceptibility to certain food allergens. A contact sensitivity to mercury, found in many of the surgical lubricants, and the absorption of phenolphthalein, frequently used in laxatives, may cause local sensitization and pruritus.

Psychogenic Factors

The importance of psychogenic mechanisms should never be overlooked in anal pruritus. Nearly every patient with an intractable anal itch presents a history of episodes causing tension. The relation of fatigue and worry can be noted in every patient and financial upsets, family maladjustments and frustrations are frequently observed. A patient with a long-standing anal pruritus usually develops a fixation on the anal area to such an extent that any upsetting influence to his existence is reflected by an anal itch, and his entire attention may be directed either to the actual itching or to the anticipation of the next episode of difficulty. This fixation may become so serious that the patient is on the verge of complete mental collapse. Such patients are desperate for lack of rest, are completely incapacitated and require immediate and serious attention.

Stokes mentions the anal erotic type of anal pruritus, which we have encountered in a small number of patients, usually young men. Sexual problems may enter into many of these cases.

Anal pruritus was an extremely rare disease in the Armed Forces as compared with its incidence among civilians. In my experience, which was largely confined to combat infantrymen but included many thousands of hospital admissions, I recall only one patient presenting an intractable anal pruritus; he was obviously maladjusted, and his one desire was to be transferred out of the

combat zone. The majority of these men, experienced infantrymen, had the highest morale and were too busy and occupied most of the time to develop an anal fixation and spend their time worrying and itching and scratching. It must be remembered that these men were frequently without baths or clean clothes for days at a time and were in a hot, humid climate.

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3 per cent lead acetate, is mild and helpful. Castellani carbolfuchsin paint — containing carbolfuchsin, phenol, boric acid and water, with or without resorcinol — is satisfactory in many cases, at first it should be diluted 1:2 and 1:3. Extremes of heat or cold may give prompt relief in certain acute situations.

In general, nonirritating, bland solutions are used and greases and ointments avoided. When lubrication is required, castor oil or olive oil may be helpful but should be employed sparingly. Frequently, following the continued use of potassium permanganate soaks, the skin tends to become dried out and mildly irritated. If actual fissures develop, ammoniated mercury ointment or a 2 per cent silver nitrate solution may aid healing. The coal tar preparations are at times indicated.

There are definite indications for surgery in these patients, but as our experience with this condition has increased, surgery has been used less and less. Surgery should be directed toward the removal of sources of infection and the correction of obvious local disease. Infected crypts should be drained, a contracted anal canal should be corrected and large edematous skin tags that interfere with local hygiene of the area should be removed. The routine removal of hemorrhoids relieves few patients. Anal fissures should be excised, and fistulas should be removed.

At a certain period in our experience with this condition, a number of the more serious cases were treated with alcohol injections. Both the techniques described by Stone⁴ and Buie⁵ were used. Temporary relief was obtained in all patients. Permanent relief was apparently obtained in a high percentage treated with the Buie technic, particularly when sufficient alcohol had been given to cause an actual slough, with complete destruction of the skin. The excessive scarring resulting from many of these procedures, however, was certainly not desirable. We have had a limited experience with the injection of local anesthetic-in-oil preparations. Temporary relief of anal pruritus has also been obtained following the injection of large quantities of both saline solution and distilled water. We have had no experience with the local injection of oxygen, with any of the tattooing procedures or with the Ball undercutting operation or any of its various modifications.

It has seemed to us that one factor common to all these different procedures has not been sufficiently emphasized, namely, local anesthesia to the

affected part. This gives definite relief from the scratch-itch syndrome and enables the patient to rest. The only real justification in these radical procedures is this common denominator. They should be reserved for the severe cases in which rapid complete rest and relaxation are imperative. It is our firm belief, however, that the incidence of recurrence will remain high if complete reliance is placed on these surgical procedures, and adequate attention is not given to the various factors that may be in the background and to the restoration of the perianal skin to its normal tone and consistency.

* * *

When patients with anal pruritus are first seen they should be given a brief but intelligent discussion of the subject. In this way, the patients themselves are often able to suggest etiologic factors that obviate expensive study and consultation. The patients must understand that they are faced with what may be a chronic condition. They must learn to treat themselves and to forestall recurrence of the anal itching. It should be pointed out to them that rest, relaxation and freedom from nervous tension are essential for permanent relief and that the object of local treatment is to eliminate infection and to restore an irritated, infected area to its normal state. When surgery is indicated, the definite limitations of the surgical procedure and its object should be pointed out. In many patients who present themselves with a long-standing anal pruritus for which they have been promised a cure following surgery, no attention has been given to any of the other factors that may have been responsible for the disease. The physician who regards the patient with an intractable anal pruritus as a neurotic and gives him no attention deserves little sympathy, the latter has a real disease that can be serious and disabling, but with a reasonable appreciation of the responsible factors and an intelligent approach to the treatment of the patient and the local condition, satisfactory results for this distressing condition can be achieved.

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REFERENCES

- 1 Stokes, J. H. Clinical analysis of pruritus ani. *Internat. Clin.* 1:147, 158, 1940.
- 2 Hill, M. R. Etiologic relationship between dermatophytosis and pruritus ani. *Tr. Am. Proct. Soc.* 41:210-222, 1940.
- 3 Terrell, E. H. and Shaw, F. W. Observations on fungal infections of perianal skin and rectum. *South. M. J.* 21:887-889, 1928.
- 4 Stone, H. B. Pruritus ani: treatment by alcohol injection. *Surg., Gynec. & Obst.* 42:565, 1926.
- 5 Buie, L. A. *Proctoscopic Examination and the Treatment of Hemorrhoids and Anal Pruritus*. 178 pp. Philadelphia: W. B. Saunders Company, 1931.

MEDICAL PROGRESS

ABDOMINAL SURGERY (Concluded)

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BOSTON

APPENDICITIS

Keyes and Cook⁴⁷ discuss the differential diagnosis in acute appendicitis in the presence of diarrhea. This combination occurs rarely but often enough to be kept in mind, especially in children or when the inflamed appendix is adjacent to the rectal wall. In appendicitis the pain is not relieved by the passage of a stool or flatus with or without enemas, whereas temporary complete relief is always thus obtained in gastroenteritis. Vomiting is more frequent and more prolonged in gastroenteritis, and the white-cell count is usually higher in appendicitis. Tenderness in the pelvis on rectal examination is diagnostic of appendicitis.

Fifty patients with proved appendiceal peritonitis were treated with massive doses of penicillin by Crile.⁴⁸ Half the cases were considered to be generalized peritonitis, and the others were localized. Eight patients had palpable masses at the time of entry, and 25 had masses during the course of observation. Twenty-three were treated conservatively, 22 had immediate appendectomy, and 5 had exploration only. After experience with smaller doses, Crile concluded that it was necessary to give 100,000 units of penicillin every two hours for two to six days, or until clinical signs had abated, followed by smaller doses for three or four additional days. The average period for the large doses was four days. Crile believed that the patients treated conservatively did better than those operated on immediately. A strict Ochsner regimen was carried out, with continuous gastric suction until normal peristalsis returned. There was a notable lack of ileus in the group. Masses disappeared under the treatment, and none had to be surgically drained, some of the pelvic abscesses, however, may have drained spontaneously through the rectum. Thirty-six per cent of the appendectomy wounds became infected, but were not tender and usually were not serious. There was one death in the group from mesenteric thrombosis. Experimental data are offered in support of the rationale for the large dosage used. This was based on the apparent inhibiting influence of *Escherichia coli* on the effect of penicillin.

It is quite probable that future reports on the use of streptomycin in such cases may be even more

spectacular. It should be borne in mind that Crile's patients had accepted methods of treatment hitherto found useful, in addition to the penicillin. Furthermore, the results in these cases, which occurred in military personnel, are compatible with earlier statistics concerning optimum recoveries for a similar group.

The differential diagnosis of acute appendicitis and acute, nonspecific mesenteric adenitis is ably presented by Aird.⁴⁹ *Tabes mesenterica* is more frequent in children and adolescents but may occur at any age. A history of acute infection — particularly of the throat — preceding the attack is often obtained. The pain is colicky, with relief between spasms. The temperature is usually higher, and there is more associated nausea and vomiting than is generally seen in appendicitis. The localization of the tenderness is above McBurney's point and slightly to the right of the umbilicus, discomfort on palpation extending from this region diagonally toward the left upper quadrant. This distribution of tenderness follows the course of the small-bowel mesentery. Discomfort on rectal examination is absent. The white-cell count is frequently lower than that usually found in appendicitis but may be high, with an increase in polymorphonuclear leukocytes. Aird suggests a virus infection as the etiologic agent, based on negative cultures from biopsied lymph nodes in the acute phase of the disease. He states that spontaneous recovery within forty-eight hours is the rule, a history of repeated attacks is frequent.

Although appendectomy does not appear to affect an acute mesenteric adenitis, it must be borne in mind that the differential diagnosis is not always possible. It is safer to explore many of these patients and remove the appendix than it is to overlook a true appendicitis with bizarre symptomatology and physical findings. Future attacks, if they occur, do not cause the same alarm to the patient, his family or the physician after the appendix has been removed. Furthermore, there is considerable evidence of a reduction in acute abdominal episodes due to mesenteric adenitis after appendectomy.

According to Etherington-Wilson,⁵⁰ 80 per cent of the cases of torsion of the great omentum are diagnosed preoperatively as acute appendicitis. The literature yielded 190 cases of this condition, and the author reports 4 cases of his own. Twisting of the

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great omentum may be complete or partial, the latter at times being represented by a single strand. The strangulation of the blood supply may also be partial or complete. The torsion may be unipolar, representing the primary or idiopathic type, or bipolar from a secondary fixed point. There were 73 cases of the primary type, which were exclusively intra-abdominal and without known cause. The secondary rotations may be unipolar or bipolar, occurring as a result of omentum fixed within a hernial sac, adhesions or deformity and caused by past or present inflammation. The condition is usually acute but may be subacute or chronic. Men between twenty and fifty years of age are generally affected. A combination of factors is probably responsible. These include abnormal peristalsis, contractions of the abdominal wall and diaphragm, sudden twisting or jerky motions of the body, direct blows on the abdomen, omental disfigurements by tumors, overloading or uneven fat deposits, pedicle formation, scarring, raggedness, adhesions, bipolar attachments and displacement of the omentum during operations for abdominal tumors.

THE STOMACH AND DUODENUM

Ladd et al.⁵¹ report the experience with congenital hypertrophic pyloric stenosis at the Children's Hospital, Boston. From 1915 to 1945 a total of 1145 cases were treated, 588 patients were admitted in the first twenty years covered in this report. There were 35 deaths in this group — a mortality of 5.95 per cent. In the ten-year period from 1935 to 1945, there were 577 cases with 5 deaths — a mortality of 0.89 per cent. There were no deaths in the last 225 cases. The value of preoperative preparation, ether anesthesia and the Robertson gridiron incision is emphasized.

Hobbs and Cohen⁵² collected from the literature 40 cases of gastroduodenal invagination and presented an interesting case report of a sixty-one-year-old woman whose intussusception was due to a submucous lipoma of the stomach. Reduction and sleeve resection resulted in recovery. The authors stated that lipomas constitute about 3 or 4 per cent of all benign tumors of the stomach, and they found only one other report of invagination due to lipoma. Prolapsing mucosa, pedunculated adenomatous polyps, pancreatic rests and leiomyomas appear to be the most frequent etiologic agents.

Moses⁵³ collected 150 cases of diverticulum of the stomach. The symptoms are similar to those of ulcer, and the diagnosis is made by roentgenographic studies. Relief is obtained by excision of the diverticulum. Walters⁵⁴ discusses the subject and adds 3 new case reports of this lesion. He refers to an earlier report of 2 cases from the Mayo Clinic.⁵⁵ Brown and Priestley⁵⁶ cite a case of diverticulum of the stomach associated with acute massive hemorrhage.

The experience with carcinoma of the stomach at the New Haven Hospital is reported by Lawrence and Kay.⁵⁷ They compare two series of cases in the decades from 1920 to 1940 and find that the patients did not report to the hospital earlier in the latter group, however, the resectability had increased, and the operative mortality had decreased. There was a 40 per cent loss owing to obvious inoperability or to the patient's refusal of operation. The lesions in 35.5 per cent of patients explored were not resectable, 8.8 per cent of patients were lost through operative mortality, whereas 9.3 per cent gradually declined and died after leaving the hospital. Of 208 patients admitted, 4.4 per cent were alive and symptom free at the end of five years, and 2 per cent died of other causes. There was a corrected salvage of 21 per cent in the 48 patients undergoing resection.

Reiteration of the importance to the physician and the layman of early diagnosis and radical treatment in cancer of the stomach is warranted. Temporary relief of indigestion by an ulcer regimen and advertised remedies is misleading. Every effort should be made to study these patients properly and to institute correct therapy before the tumor is out of bounds. The most frequent fault is the conservative treatment of middle-aged people for an ulcerative lesion of short duration. The relief of symptoms often seen without disappearance of the ulcer results in the false impression that benign ulcer is the cause, and the chance for cure is lost.

Waugh and Fahlund⁵⁸ report 77 cases of total gastrectomy by the abdominal approach from the Mayo Clinic, with an over-all mortality of 44.2 per cent. The mortality rate dropped to 3.2 per cent in 44 patients operated on between 1940 and 1943 but rose again to 20 per cent during 1943. The authors point out the value of experience in this field of surgery as being the chief factor in reducing the operative risk. Over 50 per cent of their patients who survived lived for more than two years.

Smithwick⁵⁹ reported 10 cases of total gastrectomy, with emphasis on an aseptic anastomosis between the esophagus and the jejunum by means of a special clamp he has devised. One patient was alive and well ten and a half, and another five and a half years after operation. There was no operative mortality in the 7 cases in which the aseptic technique was used.

Lahey,⁶⁰ in a discussion of Smithwick's paper, reviewed the experience with total gastrectomy by the abdominal approach in his clinic. In 92 cases 2 patients survived for over five years after this procedure for lymphosarcoma of the stomach. The mortality rate has been reduced materially in recent years.

Kelly⁶¹ reported the case of a patient who was alive and well seven and a half years after total resection for carcinoma of the stomach. The patient developed primary anemia after some years and

as restored to health by the institution of liver and iron therapy

Malignant lesions of the duodenum are discussed by Dixon et al,⁶² who found a total of 49 cases, exclusive of those arising in the papilla of Vater, in the records of the Mayo Clinic. Operation was performed in 45 cases, and 4 were revealed at autopsy. There were carcinomas in 44 cases, sarcomas in 2, a lymphangioendothelioma in 1 and associated carcinoma of the stomach in 2. Obstruction was the prominent feature in 38 patients, whereas anemia was the prevailing finding in 6. The mortality from exploration and palliative procedures was 22 per cent. Segmental resection was performed in 4 cases, and local excision in 1, with 10 deaths, and in the 4 patients subjected to radical resection, there was death in 1. One patient was alive and well six years after operation. Interestingly enough, another patient lived for seven years after gastroenterostomy before succumbing to the disease.

In a collective report on duodenal ulcer in England and Wales, Wood⁶³ states that there were 43,000 fatal cases of this lesion in the decade before World War II and that 200,000 new cases occur each year in those countries. He mentions the increase in ulcer during the London Blitz and emphasizes the mental and psychic elements in the etiology. He agrees that the problem is primarily medical, surgery being reserved for complications. Although extensive resection is regarded as the best method of treatment in properly selected cases, he has observed reasonably favorable results in a limited number of cases treated by the method of Somervell.

Somervell⁶⁴ describes his technic of interrupting five sixths of the blood supply to the stomach, in addition to posterior gastroenterostomy, as a method of treating duodenal ulcer. He compares 400 patients so treated with 300 who had been subjected to subtotal gastrectomy. He states that gastric acidity remained lowered for five years by his procedure, with only 1 case of anastomotic ulcer. There were 7 cases of stomal ulcer in the gastrectomized patients. This is similar to the early attempts to cure hyperthyroidism by progressive interruption of the blood supply to the gland. It must be borne in mind that, in interruption of the blood vessels to the stomach, the influence of the altered nerve supply may also have a bearing on the results.

Dragstedt⁶⁵ has revived interest in vagus resection for the cure of duodenal ulcer. Much enthusiasm is being demonstrated in this approach. The immediate results at the Massachusetts General Hospital in nonobstructing duodenal ulcer are impressive. If this operation, performed transthoracically, proves permanent, it will offer a simple solution to the problem. We are watching with considerable reservation the vagus interruptions below the diaphragm, because of the difficulty of exposure of the nerves

and the limited segments that can be removed by this route.

Stomal obstruction following gastroenterostomy is discussed by Gray and Sharpe,⁶⁶ who stress the two types met—one developing in the first few days and mechanical in origin, and another occurring from the seventh to the tenth postoperative day. If the mechanical arrangement is at fault, it may need operative correction. In the later, functional type jejunostomy for feeding will take care of the situation. Experience and careful technic of operation are regarded as obviating most of these difficulties.

Alesen⁶⁷ has devised an absorbable fenestrated tube made of beeswax, petroleum jelly, powdered elm bark and merthiolate with a melting point of 85°C to be incorporated within the gastroenterostomy stoma. He believes that early obstruction is the most important to overcome and that this framework is sufficient for this purpose. The tube, which disintegrates as the elm bark expands, disappears from the stoma in ninety-six hours.

Usually, early obstruction responds to decompression of the stomach segment by gastric suction through a nasal catheter. The late obstructions are extremely troublesome in my experience, occurring frequently in depleted patients. A proximal jejunostomy tube, whose tip lies in the stomach, has been used with complete satisfaction in over 300 cases. Minor complications have arisen, but none that offset the comfort and safety of the procedure.⁶⁸ No fatal cases have resulted from the use of this method of decompression. In many cases a jejunostomy for feeding is also used, particularly in patients with prolonged obstruction and resultant malnutrition.⁶⁹

Three excellent articles on the feeding of patients in preparation for surgery and during convalescence have appeared. All present variations of mixtures containing skimmed milk, skimmed-milk powder, Amigen, eggs, soy-bean flour, sucrose and salt. Varco⁷⁰ believes that patients who have lost weight should be treated by the addition of 5000 to 6000 calories of this liquid nonresidue mixture daily to the hospital diet. He states that it requires ten to twelve days of preparation for a weight loss of 20 per cent, three weeks for one of 25 to 30 per cent and a month for a loss above 35 per cent. The liquid is kept beside the patient, who is encouraged to take as much as he will. If he cannot take it voluntarily, it is introduced through a nasal tube by gravity. After this preparation, patients appearing in a depleted condition withstood major operations on the stomach or colon much better than those in an earlier series not treated in this manner.

Riegel et al⁷¹ and Lund⁷² have also outlined the nutritional requirements of patients, with particular emphasis on protein. The formulas vary slightly, and the daily caloric values are based on maintenance rather than on the correction of previous

weight loss, as stressed by Varco.⁷⁰ Many variations can be worked out, and some of the mixtures appear to be more palatable than others. The viscosity can be reduced to allow for jejunal feedings by the Murphy drip. Vitamins and liver extract can be added.

Fewer problems are involved in patients who can take nutritional mixtures or properly prepared food either voluntarily or by gastric or jejunostomy tube than in those who require intravenous feeding as the main source of nourishment. So far, there seems to be a limit to the amount of carbohydrate and Amigen that can satisfactorily be used by this route. Further purification of the constituents employed for intravenous feedings and a better understanding of their management are needed.

Custer and his associates⁷¹ have studied the problem of the so-called "dumping stomach" following subtotal gastrectomy. They believe that the symptoms of weakness, generalized and unpleasant sensation of warmth throughout the body, a cold diaphoresis of the face (particularly of the forehead) and cardiac palpitation after eating are due to the rapid emptying of the stomach into the jejunum. They found that 5.6 per cent of 500 patients studied complained of one or more of these symptoms, some of them obtained relief by lying down after eating, and many were finally relieved. This ultimate relief is explained on the theory that the jejunum becomes adjusted to the early deposit of food, and it is recommended that patients be instructed to experiment with the following measures for relief: to lie down after eating, to take 0.024 gm ($\frac{3}{8}$ gr) of ephedrine with two or three soda crackers before meals, 30 cc of cream or 45 cc of olive oil before meals, six small meals daily, a dry diet, and 10 drops of dilute hydrochloric acid half an hour before eating.

All who have seen many patients after gastrectomy are at a loss to explain the variation in their state of well-being. We found that 87 per cent of patients with duodenal ulcer were well after subtotal gastrectomy.⁷⁴ Women were likelier to complain of weight loss and discomfort after eating than men. I am not convinced that rapid emptying of the stomach remnant is the whole explanation of these symptoms. To be sure, postprandial discomfort is a more frequent complaint after total gastrectomy than after subtotal, but many of these patients eat well and without distress and a few are hungry. There seems to be a reflex in some cases that may be based on changes in the autonomic nervous system. I am sure that many of the rapidly emptying stomach segments create no symptoms.

Perman,⁷⁵ of Stockholm, informs me that if these manifestations are severe and the patient is invalidated by them, relief can be obtained by disconnection of the gastrojejunostomy and the establishment of a gastroduodenostomy. This appears to be a logical solution, since the food then passes over a more nearly normal route. The Billroth I procedure

can rarely be done satisfactorily at the time of adequate subtotal gastrectomy for duodenal ulcer, but doubtless can be quite easily accomplished at a later date, when the elements of inflammation in the duodenal stump have disappeared.

THE SMALL INTESTINE

A review of the literature by Williams and Walker⁷⁶ has revealed 300 cases of diverticulum of the jejunum. Two case reports of their own are added, one of which had been studied repeatedly over a number of years for pain and fullness in the upper abdomen, with negative findings. Finally, a diverticulum of the jejunum was diagnosed by roentgenograms, and relief of symptoms was obtained following excision of the lesion. The other patient was admitted with an acute abdominal condition and a pelvic mass. On exploration, bilateral ovarian cysts with twisted pedicles were removed, and a perforated diverticulum of the jejunum was excised. Other diverticula were noted in a 50-cm segment of the jejunum, which was successfully resected six weeks later. In both cases, on microscopic examination, the diverticula contained all the normal structures present in the jejunum.

Atwood⁷⁷ observed 37 cases of Meckel's diverticulum in 69,000 admissions to the Truesdale Hospital. He presents an excellent review of the developmental background of the lesion and discusses the causes of small-bowel obstruction associated with it. He gives a case report of intussusception due to invagination of a Meckel's diverticulum.

Two cases of repeated massive hemorrhage, with the passage of bright-red blood by rectum, due to neurofibromas of the ileum, are reported by Baker and Halley.⁷⁸ After excision of these tumors, no intraluminal ulceration was revealed in the specimens. This feature is unusual, and it seems unlikely that such a large amount of blood could have been lost except through an open vessel within the lesion. Similar tumors frequently found within the stomach become umbilicated in the central portion, and these depressions lead to an easily recognized open artery if the specimen is removed during or shortly after excessive bleeding.

Moses⁷⁹ gives an excellent discussion on acute small-bowel obstruction. He stresses the fact that most of these patients are admitted to the hospital in an acutely depleted state and therefore should usually not be subjected to immediate surgery. Careful and intelligent attention to the correction of fluid and electrolyte balance and shock is the first consideration. In patients who cannot be brought out of shock, operation offers no additional hope for cure. Usually, these patients can be made ready for surgery in a period of hours, and preoperative preparation should not be prolonged beyond the optimum period for intervention. Moses reports 118 patients admitted, with 10 deaths, 90 were operated on, with

deaths Of the 14 requiring resection of gangrenous segments, 3 died

Foissie⁸⁰ emphasizes the high incidence of small-bowel obstruction occurring in veterans after recovery from abdominal wounds This late complication is bound to occur frequently after the penetration and repair of the abdominal viscera

Calihan, Kennedy and Blain⁸¹ review the experience with acute intestinal obstruction at Johns Hopkins Hospital for a ten-year period They found that 20 per cent of 204 patients succumbed fifteen-five per cent of the deaths were due to peritonitis The duration of the obstruction was a vital factor in recovery Strangulation, followed by gangrene, and perforation were the primary causes of the fatal peritonitis On the basis of experimental work in the same clinic by Blain and Kennedy,⁸² Calihan et al believe that antibacterial therapy, particularly with penicillin, will materially reduce the mortality in acute small-bowel obstruction Dogs with isolated loops of small intestine treated with penicillin lived twice as long as control animals With penicillin, the strangulated bowel became thickened, so that gangrene and perforation were delayed They believe that their evidence points toward the bacterial theory, rather than toxic elements within the strangulated loop of bowel, as the chief cause of death

Harris⁸³ reports the use of a single-lumen tube with a mercury-weighted balloon for decompression of the small bowel This tube is of smaller outside dimensions than an effective double-lumen tube and yet has a larger lumen He advocates the use of 4 cc of mercury in the balloon and calls attention to the difficulty met in withdrawing this balloon through the pylorus In two cases the mercury was spilled within the bowel without harm to the patient The tube was occasionally allowed to pass intact through the rectum

The members of the resident staff of the Massachusetts General Hospital have preferred this new tube to the Miller-Abbott tube They find it easier to get through the pylorus and that decompression of the obstructed loops of bowel is more quickly accomplished By using the laws of gravity, there has been little trouble in causing the mercury to flow in the right direction within the balloon when the tube needs to be removed Less than 4 cc of mercury is often enough, and this amount is seldom troublesome

Another single-lumen weighted tube has been described by Cantor,⁸⁴ who recommends more and larger fenestrations in the tube The high openings in the tube are designed to pick up secretions from the stomach, as well as at intervals along the intestine It appears that the benefit of the principle of the decompression tube may be lost by this method, since the normal secretions above the obstructed loop contain valuable chemical elements that are absorbed if not removed Also, this tube

prevents the absorption of water, nutritious fluids and electrolytes that can often be administered while the decompression tube is in place

THE COLON

Schlotthauer⁸⁵ calls attention to the familial tendency in diverticulosis of the colon He reports a family of 7 brothers, all of whom were afflicted with this ailment Two sisters in the family did not have diverticulosis Reports in the literature indicate the incidence of this disorder to be from 2 to 5 per cent of the population Certainly, this figure is much too low for persons beyond middle age

Meyer et al⁸⁶ have given a good program for the preparation and aftercare of the patient in colon surgery They cleanse the bowel with cathartics and enemas and then use succinylsulfathiazole (Sulfasuxidine) for several days They take pains to bring about a chemical balance and adequate blood replacement. Spinal anesthesia is preferred Open primary anastomosis after resection of the remaining colon was carried out in 25 patients, with 1 death from embolism Early mobilization is stressed Proximal decompression is omitted Wounds are closed primarily with interrupted wire sutures Patients averaged thirteen days in the hospital after operation

Thomson and Daland⁸⁷ report the use of phthalylsulfathiazole (Sulfathalidine) in the preparation of patients with cancer of the colon and rectum, 1 gm of the drug being given every four hours for five or six days preoperatively The patients were usually well prepared for surgery, and the semisolid state of the fecal matter still in the colon was considered preferable to the more liquid effect of succinylsulfathiazole In spite of the slipping back into the peritoneal cavity of the colostomy in 2 cases, one of which was not recovered for eight hours, there was only 1 death in the series of 49 cases This fatal case occurred following resection of the splenic flexure after a cecostomy decompression for complete obstruction The effect of the phthalylsulfathiazole was thereby thwarted, and death resulted from peritonitis Sulfadiazine was given intravenously after operation Primary anastomosis was done in all lesions of the colon

Segmental resection in the left colon with primary aseptic anastomosis in 50 cases is reported by Waugh and Custer⁸⁸ There were 2 deaths in the group The Rankin three-bladed clamp was employed as the basis of the anastomosis The hospital stay in this group was greatly reduced, the safety of the procedure demonstrated, and the short morbidity emphasized when compared with a large group of patients treated by exteriorization operations

Another report of primary anastomosis following colon resection is presented by McMillan⁸⁹ In 27 consecutive cases in which operation was performed, there was 1 death from pulmonary complications

He stresses the use of two rows of interrupted non-absorbable sutures in the anastomosis. The patients averaged eighteen days in the hospital.

It is interesting to those who have always used primary anastomosis following resections of the colon to find such a general interest in this procedure. Obstructive resections and other exteriorization methods have been satisfactory to many surgeons. It is creditable that the shorter period of disability from primary anastomosis has not increased the risk in the hands of surgeons using the various aids in preparation, anesthesia, suture material, operative technic and aftercare now at their disposal. I believe that delayed wound closure is a safeguard in addition to those mentioned above.

Olsson⁹⁰ emphasizes the need for careful examination of patients with cancer of the colon. The percentage of multiple lesions, in his opinion, is much higher than is usually believed. In one year, he found between 50 and 60 cases during examination of 700 or 800 patients. In 5 cases multiple lesions were found.

In 42 out of 220 patients with cancer of the colon and rectum, Sugarbaker⁹¹ found involvement of other structures that could be removed. He reports a resectability rate of 78 per cent in a group of patients coming from a district where advanced disease, with weight loss and so forth, was the rule. Resectable extensions were found in the abdominal wall, uterus, urinary bladder, prostate, vagina, iliac vessels, ureter and femoral nerve. The vagina was involved more frequently than the prostate, probably owing to the thick fascial covering of the latter. Patients with other structures involved by continuity had symptoms of cancer of the bowel an average of fifteen months as against thirteen months in those without these extensions. The mortality rate in 72 patients in whom no other structures were involved was 9 per cent, whereas in the other group 19 per cent died, 19 patients with involvement to neighboring structures were alive two to five years after operation.

Young and Cole⁹² present some interesting experimental evidence that intraperitoneal succinylsulfathiazole and phthalylsulfathiazole may be useful when the peritoneal cavity is contaminated by fecal matter. These drugs were absorbed more quickly and created less adhesions than other sulfonamides. No toxic reaction was evident in dogs receiving 1 gm per kilogram of body weight. The proved effect on *Esch coli* by the oral use of succinylsulfathiazole and phthalylsulfathiazole makes it logical to try these drugs intraperitoneally when indications arise. Young and Cole have treated a small group of patients with 0.1 gm per kilogram of body weight without harm and suggest that larger intraperitoneal doses are probably safe.

It is interesting in this connection that Poth et al⁹³ have found that penicillin inhibits the action of phthalylsulfathiazole and does not seem to affect the

properties of succinylsulfathiazole, no explanation being available for this antagonism.

An excellent discussion on the management of the permanent colostomy is presented by Miles and his associates⁹⁴. The daily colostomy enema or wash out seemed to be favored by the majority. A few preferred to let Nature take its course. Some believed that patients could train their colostomes to function at a certain hour each day. There was little support of the use of bags or cups. Miles seemed to give the most logical advice for these patients. He recommends a daily wash out of the colon with 750 cc (1½ pints) of plain water at 80°F. He stresses the fact that hot water creates inertia of the muscular coat of the colon. Enemas should be introduced with the patient lying down, so that the muscles will be relaxed. He recommends finger dilation of the colostomy opening daily for a month, once a fortnight for two months and, finally, once a month for six months. After this, there is little tendency for contraction to take place. He uses a simple belt for support and disapproves of bags and cups, which produce prolapse, edema and bleeding of the mucous membrane.

REFERENCES

- Keyes E L and Cook M M. Diagnosis of acute appendicitis in presence of diarrhea. *Arch Surg* 52:429-444, 1946.
- Crile G, Jr. Peritonitis of appendiceal origin treated with massive doses of penicillin. *Surg, Gynec & Obst* 83:150-162, 1946.
- Aird, I. Acute non specific mesenteric lymphadenitis. *Brit M J* 2: 680-682, 1945.
- Etherton-Wilson, W. Torsion of great omentum: report of four cases. *Brit J Surg* 33:142-146, 1945.
- Ladd W E, Ware, P F and Pickett, L K. Congenital hypertrophic pyloric stenosis. *J A M A* 131:647-651, 1946.
- Hobbs W H and Cohen, S E. Gastroduodenal invagination due to submucous lipoma of stomach. *Am J Surg* 71:505-518, 1946.
- Moses W R. Diverticula of stomach. *Arch Surg* 52:59-65, 1946.
- Walters, W. Diverticula of stomach. *J A M A* 131:954-956, 1946.
- Schmidt, H W and Walters, W. Diverticula of stomach. *Am J Surg* 52:315-318, 1941.
- Brown P W and Priestley J T. Massive and recurrent gastro-intestinal hemorrhage from diverticulum of stomach. *Proc Staff Meet, Mayo Clin* 13:270-272, 1938.
- Lawrence, E A and Kay, J H. Carcinoma of stomach: ten year survey made in general hospital. *Surgery* 19:505-514, 1946.
- Waugh, J M and Fahland, G T R. Total gastrectomy. *Surg Clin North America* 25:903-917, 1945.
- Smithwick, R. Total gastrectomy. *New Eng J Med* (in press).
- Lahey F H. Discussion of Smithwick⁵⁹.
- Kelly C. Discussion of Smithwick⁶⁰.
- Dixon C F, Lichtman, A L, Weber, H M., and McDonald, J R. Malignant lesions of duodenum. *Surg, Gynec & Obst* 83:83-95, 1946.
- Wood W Q. Treatment of duodenal ulcer. *Edinburgh M J* 51:433-450, 1945.
- Somervell, T H. Physiological gastrectomy: operation of ligation of arteries of stomach to relieve hyperacidity and to prevent recurrent ulceration after gastro-enterostomy. *Brit J Surg* 33:146-152, 1945.
- Dragstedt L R. Section of vagus nerves to stomach in treatment of gastro-duodenal ulcer. *Minnesota Med* 29:597-605, 1946.
- Gray H K, and Sharpe, W S. Gastric retention after posterior gastroenterostomy for duodenal ulcer: prevention and treatment. *Ann Surg* 123:397-409, 1946.
- Alesen, L A. Safety factor in gastric resection: preliminary report. *Surgery* 19:220-222, 1946.
- Allen A W, and Donaldson, G A. Jejunostomy for decompression of postoperative stomach. *Surgery* 15:565-568, 1944.
- Allen A W and Welch C E. Jejunostomy for relief of malfunctioning gastroenterostomy stoma. *Surgery* 9:163-182, 1941.
- Varco R L. Preoperative dietary management for surgical patients: with special reference to lesions of stomach and duodenum. *Surgery* 19:303-378, 1946.
- Riegel, C, Koop C E, Grigger, R P, Rhodes, J E., and Bullitt L. Protein requirements of surgical patients during postoperative period. *S Clin North America* 25:1096-1105, 1945.
- Lund C C. Protein nutrition of surgical patients. *Surg Gynec & Obst* 83:259-261, 1946.
- Custer, M D, Jr., Butt, H R. and Waugh J M. So-called "dumping syndrome" after subtotal gastrectomy: clinical study. *Ann Surg* 123:410-418, 1946.

- Allen, A. W., and Welch, C. E. Subtotal gastrectomy for duodenal ulcer *Ann Surg* 124 688-707, 1946
- Perman L. Personal communication
- Williams C. and Walker, J. B. Diverticula of jejunum — with report of two cases *Virginia M Monthly* 73 212-215, 1946
- Atwood W. G. Meckel's diverticulum with report of case of intussusception due to its invagination *Am Eng J Med* 234 329-332, 1946
- Baker H. L., and Haller H. Neurofibroma of small intestine with massive hemorrhage. *Am Surg* 123 1067-1074, 1946
- Moses W. R. Acute obstruction of small intestine report of one hundred and eighteen cases. *Am Eng J Med* 234 76-81, 1946
- Forsie P. S. Intestinal obstruction following abdominal battle wounds. *Am Eng J Med* 234 498-500, 1946
- Caliban, R. J. Kennedy J. D. and Blain A. III. Intestinal obstruction study of two hundred and four acute cases with reference to possible efficacy of anti bacterial therapy. *Bull Johns Hopkins Hosp* 79 21-33, 1946
- Blain, A., III, and Kennedy J. D. Effect of penicillin in experimental intestinal obstruction studies on strangulated low ileal obstruction. *Bull Johns Hopkins Hosp* 79 1-20, 1946
- Harris, F. I. Intestinal intubation in bowel obstruction technique with new single lumen mercury weighted tube. *Surg Gynec & Obst* 81-671-678, 1945
- Cantor, M. O. New simplified intestinal decompression tube. *Am J Surg* 72 137-142, 1946

- 85 Schlotthauer H. L. Familial diverticulosis of colon report of seven cases in one family of nine persons. *Ann. Surg* 124 497-502, 1946
- 86 Meyer L. A. Sheridan A. and Kozoll D. D. One stage 'open' resection of lesions of left colon without complementary colostomy. *Surg Gynec & Obst* 81 507-514, 1945
- 87 Thomson R. and Daland E. M. Use of phthalylsulfathiazole (sulfathalidine) in colonic surgery. *New Eng J Med* 234 431-433, 1946
- 88 Waugh J. M. and Custer M. D., Jr. Segmental resections of lesions occurring in left half of colon with primary end-to-end aseptic anastomosis, report based on 50 cases. *Surg Gynec & Obst* 81 593-595, 1945
- 89 McMillan W. M. Primary resection of malignant lesions of large bowel. *Am. J Surg* 71 502-504, 1946
- 90 Olsson O. Cancer coli multiple. *Acta radiol* 26 415-424, 1945
- 91 Sugarbaker E. D. Coincident removal of additional structures in resections for carcinoma of colon and rectum. *Am Surg* 123 1036-1046, 1946
- 92 Young J. P. and Cole W. H. Intraperitoneal administration of succinylsulfathiazole and phthalylsulfathiazole their use in prophylaxis and treatment of peritonitis. *Arch. Surg* 53 182-189, 1946
- 93 Poth E. J., Wise R. I., and Slattery M. P. Penicillin phthalylsulfathiazole antagonism. *Surgery* 20 147-149, 1946
- 94 Miles W. E. Gordon-Watson C. G. Milligan E. T. C., and Corbett, R. S. Discussion on management of permanent colostomy. *Proc Roy Soc Med* 38 691-696, 1945

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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BENJAMIN CASTLEMAN, M.D., *Associate Editor*

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CASE 33051

PRESENTATION OF CASE

A sixty-six-year-old furniture crater entered the hospital because of exertional dyspnea.

Six years before entry, the patient had had an attack of pneumonia requiring four weeks' hospitalization, during which he received sulfadiazine, and rest at home for eight weeks. During this period he had gained 20 pounds in weight, which he had maintained. On resuming work he felt "better than ever before" but noted some exertional dyspnea and night sweats. He also had an occasional nonproductive cough and two or three paroxysms of coughing daily. Two months before entry, the patient saw a local physician because of continuing dyspnea and was referred to this hospital. During the summer before entry, he lost 8 pounds, which was not unusual for him during hot weather.

Physical examination showed a well preserved man in no discomfort. The only positive findings were scattered rales over the left lung base posteriorly.

The temperature was 99°F, the pulse 70, and the respirations 18. The blood pressure was 170 systolic, 90 diastolic.

Examination of the blood disclosed a hemoglobin of 14.0 gm and a white-cell count of 15,500, with 83 per cent neutrophils, 5 per cent lymphocytes, 8 per cent monocytes and 3 per cent eosinophils.

The nonprotein nitrogen was 25 mg per 100 cc. The urine was normal.

An x-ray film of the chest showed the left hilus to be considerably increased in size and moderately elevated. Irregular linear bands of increased density extended outward into the upper middle and lower lung fields. The heart shadow was displaced to the left, and there was an inspiratory shift of the mediastinum to the left. The diaphragm moved fairly well. Within the density in the left hilus was a 2-cm sharp line, suggesting a fluid level in a small cavity.

Bronchoscopy of the right bronchial tree was negative. The left main bronchus was normal, down to the upper-lobe orifice. Close to this orifice, which appeared slightly narrowed, there was narrowing of the left main and left lower-lobe bronchi, with some fixation and a slightly nodular appearance. Several biopsies from this area were reported as showing chronic inflammation.

On the eighth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR EDWARD D. CHURCHILL. We are to discuss the case of a patient with a serious illness that led to operation. As the record stands, we must accept the facts that the symptomatology was of long duration and that all symptoms dated back to the episode of pneumonia six years before entry. It is always important to find out just what brings a patient to the doctor at the time that he summons the courage to make the trip. Nothing in the record, however, gives any lead to new symptoms or to an increase or change in old symptoms that might have led this patient to consult a physician two months prior to admission. The presenting symptom is recorded as "continued dyspnea." Even the significant fact of whether he had or had not raised blood is lacking.

DR TRACY B. MALLORY. Can you answer that, Dr Sweet?

DR RICHARD H SWEET I am impressed by the difference between the story obtained in the hospital and that obtained in my office. I have the recollection that the patient had had recent symptoms of cough and occasional staining with blood, but I may be wrong.

DR CHURCHILL Is this fact, not being given in the history, admissible as evidence?

DR MALLORY Yes, I think you had better use all the information available.

DR CHURCHILL You will admit blood spitting?

DR SWEET My recollection is that the patient had had occasional recent spitting of blood, which was intermittent.

DR CHURCHILL Not every day, and occurring within the previous few months?

DR SWEET That was my impression.

DR CHURCHILL Consequently, there was a change that brought about a visit to a physician two months before admission. There is also no note of whether the sputum was examined in the hospital. We then focus our attention on a differential diagnosis between chronic infection and neoplasm of the lung.

May we see the x-ray films?

DR JAMES R LINGLEY This is the enlarged left hilus that was described, with what looks like a fluid level in the central portion, outlining a cavity about 2 cm in size. In addition, there are linear bands of density extending upward into the upper, middle and lower lung fields. The bands are also visible in this lateral view, extending backward to the base of the upper lobe and forward into the lower lobe. The heart is slightly displaced to the left side, and fluoroscopically a note was made that there was a mediastinal shift to that side on respiration.

DR CHURCHILL Where is the cavity on the lateral film?

DR LINGLEY The fluid level is not adequately demonstrated in the lateral view. I suspect that the cavity was posterior to the hilus, but I cannot be sure.

DR CHURCHILL Was the cavity peripheral?

DR LINGLEY I cannot be sure.

DR CHURCHILL Can you localize this process in the lateral film — whether it was in the upper or the lower lobe, or both?

DR LINGLEY I think that it involved both, but it was more marked in the base of the upper lobe.

DR CHURCHILL Do you think that this is a cavity far posteriorly?

DR LINGLEY That location in general.

DR CHURCHILL In this case the differential diagnosis lies, as I have said, between chronic infection with or without an acute exacerbation and a bronchiogenic carcinoma. I am not satisfied with the history as presented in the record, because there is nothing to suggest that a new entity, such as carcinoma, had come into the picture. If we admit

the recent appearance of blood spitting, an increase in exertional dyspnea, some feeling of fatigue, some stiffness of the joints or a dozen other symptoms that might have taken this man to a physician two months before entry, I think that we are tipping the scale toward bronchiogenic neoplasm. I must raise one other question. In discussing another patient, Dr Sweet recently stressed the point that an abscess cavity in the lung of purely inflammatory origin is usually peripheral, whereas in neoplasm it may be central. If we apply that yardstick to Dr Lingley's interpretation that the cavity was centrally rather than peripherally placed, it favors carcinoma. This would have been a good case in which to try out examination of the sputum for tumor cells, but we are proceeding without sputum examination. The bronchoscopic findings were quite significant so far as narrowing and fixation of the bronchus were concerned. Such fixation is a sign that is associated with carcinoma rather than an inflammatory condition. There was no recent history of a bad cold or an attack of grippe, which might have exacerbated an old pneumonitis. A lung abscess appearing six years after pneumonia is unusual, and lacking further evidence I consider the scales weighed toward bronchiogenic carcinoma. I am willing to proceed with Dr Sweet, if that was his diagnosis, with a thoracotomy incision for inspection and probable removal of the lung.

DR MALLORY Dr Sweet, do you want to tell the operative findings?

DR SWEET Perhaps Dr Benedict would like to describe the bronchoscopy.

DR EDWARD B BENEDICT It is all given in the record. I did say "partial fixation," however — not complete.

DR SWEET I have been trying to obtain my office record because my impression was so different, and I regret that I did not review the history of the hospital record before it was presented. But, as I have said, my impression was that a definite change in the form of the cough or some expectoration with an occasional streaking of blood caused the patient to consult a physician.

I was not certain what the diagnosis was ahead of time. Dr Benedict and I have often labored over cases of this type, and in quite an appreciable number we have been forced to perform an exploratory thoracotomy. As Dr Churchill suggested, that is what we did. Before operation I was not certain whether the cavity was central or peripheral. My impression was that it was central, but it actually was peripheral. We made a thoracotomy incision and discovered that the most adherent portion of the lung was in the region of the dorsal division of the lower lobe, the adhesions were of the character that we have learned to associate with chronic infection. They were so dense that one could not develop a plane of cleavage. The lung had to be separated with a knife, but I did not believe that

here was a special indication for entering the extra-pleural fascial plane. In separating that portion of the lung from the chest wall, however, I opened into the cavity, which presented the usual appearance of a chronic inflammatory cavity. It did not look like a lung abscess or carcinoma, but in the region of the hilus there was an indurated area that I thought was carcinoma. The structures about the hilus were almost typical of carcinoma — so much so that when I began to dissect about the hilus, I said, "This is probably an inoperable case, even if I can do a pneumonectomy, it is incurable." There were firm, hard lymph nodes that were beyond the limit of my ability to reach. I completed the pneumonectomy, and I was sure the lung and lymph nodes would show malignant disease. The perihilar tissue — not only the nodes, but also the areolar tissue — was adherent. It was difficult to develop the vessels. There was a good deal of contraction of structures, and the phrenic nerve was pulled over.

CLINICAL DIAGNOSIS

Bronchiogenic carcinoma of lung?

DR CHURCHILL'S DIAGNOSIS

Bronchiogenic carcinoma of lung

ANATOMICAL DIAGNOSES

Chronic pulmonary tuberculosis

Tuberculosis of bronchial lymph nodes

PATHOLOGICAL DISCUSSION

DR SWEET This case was different from the cases of tuberculosis in which we have operated, the majority of which have shown a free hilus, which could be dissected with relative ease. I should like to point out that in the field of thoracic surgery there is an analogy with abdominal surgery in cases of this sort. Often, I have been confronted, as other surgeons have, with the difficulty in differentiating an inflammatory mass in the cecum or sigmoid and a carcinoma. I remember a case that was discussed here of a patient on whom I had operated, performing a right colectomy in the belief that I was dealing with carcinoma. Dr Castleman came over to see it and could not tell what it was. It turned out to be an appendiceal abscess. Dr Allen remarked that he had had that experience himself. In other words, on the operating table it is difficult to differentiate some cases of chronic infection or tuberculosis of the colon and carcinoma, and the same thing is true of the lung.

DR MALLORY The lung we received showed extensive tuberculosis with a large cavity at the apex of the lower lobe. The lymph nodes at the hilus were also involved with firm, dense, fibro-caseous tuberculosis.

CASE 33052

PRESENTATION OF CASE

First admission A forty-eight-year-old machinist was admitted to the hospital because of a productive cough.

At the age of twenty-five the patient had had "double pneumonia" and typhoid fever, and he had suffered from influenza during the 1918 epidemic. At the age of thirty-one a rib resection had been performed because of a left-sided empyema. The patient stated that during the succeeding two weeks he could "blow smoke through a hole in his back", this closed during the next two and a half months, however, and he fared well except for a chronic dry cough and occasional colds that settled in the "left bronchial tubes." The recent cough had begun nine months previously, when he had had a severe cold progressing to pneumonia with a temperature of 101°F and a cough productive of "heavy pus" without blood or chest pain. During the two weeks of confining illness, he lost 17 pounds. Following this he continued to have a cough productive of one or two tablespoonfuls of yellow-white, sometimes foul-smelling, sputum, especially in the morning. He also complained of persistent weakness and general malaise. Six months before entry the feet became chilled and the patient was again confined to bed for three days with chills and fever. A similar episode occurred two months later. The patient had never coughed up blood since the original empyema.

There was no family or other history of exposure to tuberculosis. The patient had done considerable welding and had been exposed to zinc oxide.

Physical examination in the Out Patient Department three months before admission revealed that the left leaf of the diaphragm was elevated, with limited excursion, there were a soft inspiratory wheeze over the left base posteriorly and occasional crackling inspiratory rales over the same area with questionable dullness and diminished breath sounds. X-ray examination revealed a cavity filled with air and fluid in the posterior aspect of the left chest at the level of the hilus, where there was a band of increased density reaching to the diaphragm. The left lower lobe appeared to be somewhat decreased in size. In the lower portion of the cavity there was a mottled area of increased density that had the appearance of old lipiodol. There was a partial resection of the ninth rib on the left.

Three months later the patient was admitted to the hospital. The x-ray and physical findings were essentially unchanged. A tuberculin test was negative in a concentration of 1:10,000. Examination of the blood showed a red-cell count of 4,260,000 and a white-cell count 8550, with 40 per cent neutrophils, 49 per cent lymphocytes, 8 per cent monocytes, 1 per cent eosinophils and 2 per cent basophils. Repeated x-ray series were negative.

A right lower lobectomy was performed, and

pathological examination was reported as showing lung abscess with chronic pneumonitis and pleuritis. Following operation there was persistent drainage of 30 to 40 cc of foul pus from the wound without fever and despite sulfadiazine administration. X-ray examination revealed adequate expansion of the remaining lung, with no mediastinal shift. There were only a small amount of fluid and a few streaks of atelectasis at the base of the lower lobe. Lipiodol injection revealed a fistulous communication with the left lower bronchus with no intervening cavity. The patient was discharged to be followed in the Out Patient Department.

Second admission (four months later) Follow-up study in the Out Patient Department revealed the tract to have gradually closed and after two months extended only into the chest wall. A repeat x-ray examination disclosed essentially the same findings as previously with some thickening of the pleura along the left chest laterally and posteriorly without definite effusion. During the following month the patient had fever and malaise with increased drainage, the fistula reached the pleural space, but no pocket of pus was evident. Two weeks later an abscess developed in the old operative scar. It was incised and drained and found to extend to the bone. Culture revealed a few colonies of *Staphylococcus aureus*.

Two weeks later the patient was readmitted to the hospital because of a new abscess. Incision and drainage of the new area revealed an abundant growth of *Staph aureus* on culture. The patient was discharged on the seventh day.

Third admission (five weeks later) The drained areas failed to heal, and more furuncles continued to develop so that there were six different areas, most of which drained thin pus with cheesy particles that on smear and culture were negative for tubercle bacilli and showed moderate growth of *Staph aureus*. The patient was readmitted for biopsy and open drainage of the entire area.

Physical examination showed no changes in the five months since the lobectomy, except for the evident weight loss of 30 pounds and the draining sinuses.

X-ray studies with lipiodol injections of three fistulas were unsatisfactory but revealed no definite interconnection. The white-cell count was 25,000, and the red-cell count was 4,100,000, with a hemoglobin of 65 per cent. Examination of the urine showed only rare, short granular casts and 8 to 10 white cells per high-power field in the sediment.

Drainage of the area was accomplished surgically with a rib resection and secondary closure. Pathological examination of the tissue was reported as showing acute and chronic inflammation, with granulation tissue and a foreign-body, giant-cell reaction. The last x-ray film showed the seventh, eighth and ninth ribs resected posteriorly. The tenth rib was fractured, with a mottled area of decalcification.

Final admission (two months later) The patient was readmitted because of a bronchocutaneous fistula that had developed two weeks previously. He experienced considerable pain and cough during the week before admission and raised small amounts of yellow-white sputum without blood. He complained of profuse night sweats, with a temperature of 101 to 102°F, but there were no chills.

Physical examination was essentially unchanged aside from the emaciated appearance and a new bronchocutaneous fistula.

Examination of the blood revealed a red-cell count of 3,800,000, with a hemoglobin of 80 per cent, and a white-cell count of 21,700. Repeated examinations of the urine were negative. An x-ray film disclosed a small amount of periosteal proliferation of the eighth and ninth ribs and little change in the thickened pleura. Subsequent re-examinations showed a small amount of new-bone formation about the ends of the resected ribs. In addition, there was a moderately large air-containing cavity in the posterior portion of the left lung field with no evidence of undrained fluid.

In the hospital the patient continued to have pain in the ribs on the left, a spiking temperature up to 102.5°F, with profuse night sweats and continued thick yellow-green purulent drainage of the fistulas. On one occasion he coughed up "three mouthfuls" of blood. He was given testosterone and repeated blood transfusions. The white-cell count in two weeks fell to 15,000, and the red-cell count rose to 5,130,000 with a hemoglobin of 85 per cent.

Three weeks after admission an x-ray report mentioned a definite collection of fluid posteriorly in the left chest, probably at the level of the fifth rib. During the following week a new rib resection was performed.

DIFFERENTIAL DIAGNOSIS

DR F DENNETTE ADAMS The history at the time of the first admission was characteristic of bronchiectasis. At first glance it seems reasonable to suppose that this patient's trouble started at the age of thirty-one with an attack of lobar pneumonia. Empyema appearing spontaneously is rare, and the spitting of blood was probably due to pneumonia rather than to empyema. The bronchopleural fistula doubtless resulted from rupture of a small subpleural abscess. Following recovery, one might postulate that the process in the lung did not entirely clear, the patient was presumably left with some residual damage, such as an area of bronchiectasis at the site of the original pneumonia. One can assume that, as so often happens in these cases, complicating episodes following the acute upper respiratory infection consisted of repeated bouts of acute bronchopulmonary disease in the affected area. The physical signs in the thorax — dullness, elevation of the diaphragm, diminished breath sounds, and rales — are consistent with this explanation.

indicating probable pleural thickening and contraction, localized pulmonary fibrosis and bronchiectasis. The localized wheeze is confusing and cannot be accounted for. Usually indicative of partial obstruction of a bronchus, this sign is highly suggestive of emphysema. Because of the presence of trapped air, with partial bronchial obstruction, however, one expects expansion, not contraction, of the affected area of the lung, the findings should have been not dullness but hyper-resonance and prolonged expiratory rales. Examination of the lungs provided no evidence of cavitation, probably because of the deep location of the cavity.

May we see the first x-ray films?

DR LAURENCE L. ROBBINS: These are the first films taken and show the thickened pleura and an air-containing cavity, which appears to be in a dorsal division of the left lower lobe. There is a collapse—that is, a decrease in the size of the lobe—because the lobe is too small generally, but the greater portion of the trouble appears to be in the dorsal division.

DR ADAMS: Could the shadow said to have been the appearance of lipiodol be caused by any other foreign substance? We have no record of lipiodol injection.

DR ROBBINS: It could be calcification, I suppose, but it looks much more like lipiodol.

DR ADAMS: Attention must be directed to certain factors in the record that throw considerable doubt on the explanation of the illness just postulated. In the first place the patient had no trouble from the age of thirty-one until nine months before admission, when he was forty-seven and when all the acute episodes occurred, it is hard to believe that with either bronchiectasis or abscess he could have gone sixteen years with no symptoms and then have been repeatedly in trouble. Secondly, at that time, the patient lost 17 pounds within two weeks—a much greater weight loss than is usual in acute infection superimposed on bronchiectasis or in pneumonia. Thirdly, x-ray examination showed an abscess cavity that was thin walled and, although productive of sputum, gave a smaller daily output than is usual in a postpneumonic abscess. These facts force me to the conclusion that the episode nine months before entry was new and not related to the empyema and the postulated lobar pneumonia. The character of the cavity and the amount of sputum are not inconsistent with coccidioidomycosis although typically one sees even less tissue reaction around the cavity than that in this case. This disease can be dismissed on the grounds of probability, since we have no record that the patient ever resided in an endemic area.

The laboratory tests give no clues. The result of the blood Hinton test is not reported.

DR. TRACY B. MALLORY: We can assume that it was negative.

DR ADAMS: All one can say up to the time of the first operation is that the patient had an abscess of undetermined origin, probably of neither tuberculous nor postpneumonic origin.

Following operation the patient was in continuous trouble. At no time was he entirely free of draining sinuses, and after a few months, new abscesses and draining sinuses continued to appear in spite of repeated surgical measures. X-ray study disclosed evidence of bone destruction, and eventually a bronchocutaneous fistula developed. Meanwhile, the patient went downhill, with severe weight loss, increasing fever and marked elevation of the white-cell count. A further indication of his poor condition is the need for transfusions and testosterone, the latter given presumably in an effort to restore nitrogen balance. Sulfonamides and penicillin were doubtless given and proved ineffectual.

DR MALLORY: The patient received sulfonamides repeatedly. This case occurred before the era of streptomycin. Penicillin was given only toward the end of the last admission.

DR ROBBINS: This film, taken shortly after lobectomy, shows more pleural reaction than one would expect. This next film simply confirms the presence of the bronchocutaneous fistula, the lipiodol enters the left main bronchus and then goes into the portion of the upper lobe. This film was taken approximately five months after the post-operative episode, and there is an increase in the pleural reaction. The changes in the periosteum on the inner surface of the ribs, which usually go with secondary infiltration with empyema, begin to be visible. The resected ribs are again seen, and this film shows beginning new-bone formation, but it does not seem to be so marked as usual. These films show the collection of fluid posteriorly that was mentioned at the time of the final admission. I think that there is some change in this vertebra, but the films were not taken for that purpose.

DR ADAMS: What about the fractured rib?

DR ROBBINS: It does not seem to have regenerated so rapidly as they often do, and in all these films there are questionable areas of bone destruction.

DR ADAMS: Fracture because of destruction?

DR ROBBINS: No, probably the result of operative procedures.

DR ADAMS: We are confronted, then, with a patient who, nine months following an acute pulmonary infection of some kind, was found to have a lung abscess. The clinical picture did not conform to that usually seen in postpneumonic abscess. Following lobectomy, instead of getting well, as was anticipated, the patient continued to be in difficulty. The systemic reaction was severe, multiple abscesses and fistulas and eventually a bronchial fistula developed. The possibility of tuberculosis seems to be ruled out by the x-ray films and the pathological findings, as well as by the negative cultures. I should be more confident if a guinea-pig

test had also been performed and reported negative.

A chronic suppurative process due to *Staph aureus* is suggested by the repeated isolation of that organism from the pus, but I doubt whether it could be held responsible for the large number of fistulas and, in a chronic case such as this, for the severe systemic reaction. Once drainage had been established, that should have been sufficient. More help might also have been expected from the sulfonamides.

A foreign body, perhaps a sponge, is a possibility, but again one would expect a single and persistent draining sinus — not multiple sinuses.

One not infrequent disease of the lung is manifested by the appearance of multiple stubborn sinuses, and I believe this to be the cause of this patient's illness. Although typically it causes multiple small abscesses of the lung, I suppose it could produce a large one, an explanation is provided for the unusual character of the abscess — that is, for its failure to conform to the pattern of postpneumonic cavitation. This disease also readily accounts for the extreme systemic reaction, loss of weight, emaciation and high fever. In my opinion the only likely diagnosis in this case is actinomycosis.

A PHYSICIAN: Did the yellow pus have any relation to the actinomycosis? Were the sulfur granules cultured?

DR MALLORY: That is a question that often comes up. In all probability the laboratory was never asked to look for actinomycosis. The specimens were examined in the routine bacteriologic laboratory and repeatedly examined in the surgical bacteriology laboratory, and in neither were actinomycetes found, I cannot say how specifically they were looked for, however.

DR BEVERLY TOWERY: We recently had a patient in the Baker Memorial Hospital with a chronic infection of the chest wall, after two weeks' study we were convinced that she had actinomycosis, and yet

it took a week of careful search to find the sulfur granules. I have seen three cases within the year — one with recurring liver abscesses, the case that I just mentioned and another that simulated chronic gall-bladder disease — in which the patients had actinomycosis. It is essential to realize the protean nature of this infection so that its presence may be suspected more frequently and the organisms may be looked for in fresh material.

CLINICAL DIAGNOSIS

Actinomycosis of lung

DR ADAMS'S DIAGNOSIS

Actinomycosis of lung, with abscess formation and bronchocutaneous fistula

ANATOMICAL DIAGNOSIS

Actinomycosis of lung

PATHOLOGICAL DISCUSSION

DR MALLORY: At the final operation some tissue was removed in which we were able histologically to demonstrate actinomycosis. We went back over all the previous specimens, including those from the original lobectomy, and in none were we able to find organisms. The organisms are often few and far between. There is a good deal of chance in picking the right location from which to take a section. It is reasonable to assume that the history from the beginning can be explained on the basis of actinomycotic infection.

DR DONALD S. KING: Are cavities with a fluid level usually seen?

DR MALLORY: We expect multiple small cavities instead of a single cavity.

DR ADAMS: I tried to find out about that point from the literature in the short time that I had to prepare this case. Most articles merely refer to cavitation.

The New England Journal of Medicine

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Established 1828

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COMMUNICATIONS should be addressed to the *New England Journal of*
- *Medicine* 8 Fenway Boston 15 Massachusetts

POSTGRADUATE LECTURE COURSE

THE three-month Postgraduate Lecture Course given last winter and spring proved to be so popular that, in a somewhat abbreviated form, it will be repeated this year. The program has been arranged by a subcommittee of the Subcommittee on Postgraduate Education of the Committee on Postwar Planning of the Massachusetts Medical Society, in co-operation with the Massachusetts Department of Public Health. The lectures will be given on Mondays — from 5.30 to 7.00 and from 7.30 to 9.00 — and on Wednesdays — from 3.00 to 6.00 — beginning on March 3 and ending on April 23. A buffet supper will be served on Mondays between 7.00 and 7.30. As formerly, all exercises will be held at Sanders Theater, Harvard University, Cambridge.

A tentative outline of the program appears elsewhere in this issue of the *Journal*. All the topics are of general interest, and the chairmen have been so wisely selected that adequate and timely discussions are guaranteed. Of special interest is the topic for the first day — "The Medical Aspects of Atomic Warfare." The session will be presided over by Dr. Stafford Warren, professor of radiology at the University of Rochester School of Medicine, and Dr. Shields Warren, pathologist at the New England Deaconess Hospital, Boston. The former, while in the Army, served as medical director of the Manhattan Project, and the latter, while in the Navy, was director of medical research at the Bikini Test. They undoubtedly know more about the medical aspects of atomic warfare than any other persons in the world, and the program, which will include motion pictures of the Bikini Test, should provide three hours of intensely interesting instruction and entertainment.

The course is primarily intended for the practicing physicians of Massachusetts and the surrounding states, but hospital residents and interns and medical students are cordially invited to attend. All those who plan to be present are required to register, but no charge will be made other than one for those who participate in the suppers on Mondays. A copy of the final program will be forwarded to all licensed physicians in Massachusetts, and a return postal card will be enclosed requesting information concerning attendance at the first lecture, the majority of lectures and the buffet suppers. To aid the subcommittee, all postal cards should be promptly returned. Those who wish to register immediately should do so by writing to the Postgraduate Lecture Course Committee, Massachusetts Medical Society, 8 Fenway, Boston.

NATIONAL HEART WEEK

Just as modern warfare demands the active co-operation of a large segment of the civilian population, so the war against disease can no longer be left entirely to a relatively small professional body. In girding itself for a vigorous offensive against man's greatest killer the American Heart Association has undertaken a fundamental reorganization involving extensive lay participation. It is seeking not merely

to broaden its membership base but also actually to take nonmedical persons into its executive bodies up to 50 per cent of the membership of each. This means that the lay members may have an equal voice with the physicians in determining the general policies of the association. Such an arrangement cannot fail to be a stimulating one for both groups. At the same time the Scientific Council, open only to members of the American Heart Association who have made significant contributions to knowledge of cardiovascular disease, will maintain the high scientific standards of the association. Another feature of the reorganization is closer integration with the local heart associations, such as the New England Heart Association, including joint membership. Recognizing that rheumatic fever stands out as one of the most urgent unsolved medical problems of the day, the American Heart Association has accepted the responsibility of incorporating the American Council of Rheumatic Fever within its structure. The objectives of the council are to aid and guide local communities in the organization of programs designed to attack the rheumatic-fever problem, to prepare and distribute criteria for the diagnosis of rheumatic fever and rheumatic heart disease, together with recommendations for treatment and convalescent care, to educate groups of physicians, nurses, social workers, teachers and so forth and to sponsor research.

The American Heart Association will carry on the publication of the *American Heart Journal*, *Modern Concepts of Cardiovascular Disease* and special pamphlets. It will provide slides, pictures, exhibits, models and so forth for instruction and will co-ordinate programs of postgraduate education throughout the country among medical schools, hospitals and county societies. It will assist in the development and establishment of standards for accurate diagnosis, clinics, facilities for acute and convalescent hospital care, nursing care, occupational therapy, vocational guidance and medical social service, periodic health examinations and vital statistics. It will carry health education to the public, and it will aid the cardiac patient in securing employment. Finally, it will accept responsibility for stimulating, guiding, co-ordinating, sponsoring and financing research along statistical, clinical, labora-

tory and epidemiologic lines. The 1947 budget for carrying out this program is \$561,000, including \$275,000 for research.

The inauguration of the public-education program has been appropriately observed by the proclamation of National Heart Week — February 9 to 15. During this period every medium of information — the press, radio, magazines, motion pictures and special events — will be used to drive home the message that the control of heart disease is the most vital health problem confronting the public today. The campaign will be purely educational, no public drive for funds being contemplated at this time. Physicians will be well advised to be prepared to answer questions from their lay friends and patients regarding the objectives of the American Heart Association.

MASSACHUSETTS MEDICAL SOCIETY EXECUTIVE COMMITTEE OF THE COUNCIL

The Executive Committee of the Council, in regular session on January 8, 1947, approved the following recommendations submitted by the Committee on Membership:

That the following named fellows, applying for retirement and with all dues paid and in good standing, be allowed to retire under the provision of Chapter I, Section 5, of the by-laws:

Champion, Merrill E. (Suffolk), 42 Anderson Street, Boston
Cook, Philip H. (Worcester), 19 Somerset Street, Worcester
Cummin, John W. (Suffolk), 416 Marlboro Street, Boston
Hamblet, Mary L. (Essex South), 120 Federal Street, Salem
Hosley, Walter A. (Middlesex South), Salem Road, R F D, Danvers
Lakeman, Mary R. (Essex South), 108 Federal Street, Salem
MacDonald, William C. (Middlesex South), 21 Mountain Avenue, Newtonville
Thayer, Hartley W. (Middlesex South), 355 Walnut Street, Newtonville
Tucker, S. Chase (Essex South), 379 Lowell Street, Peabody

That the following named fellows, applying for resignation and with all dues paid and in good standing, be allowed to resign under the provisions of Chapter I, Section 7, of the by-laws:

Burke, Edward W. (Middlesex South), 55 Bradford Boulevard, Tuckahoe, New York
Pratt, Henry N. (Norfolk), 444 East 68th Street, New York 21, New York
Spira, Bertram (Barnstable), 626 S. Alvarado Street, Los Angeles, California
Zielinski, John B. (Bristol South), 781 Carroll Street, Brooklyn, New York

That the following named fellows, applying for resignation from the Massachusetts Medical Society but in arrears of dues, shall have these dues owed the Massachusetts Medical Society remitted under the provisions of Chapter I, Section 6, of the by-laws and shall then be allowed to resign under the provisions of Chapter I, Section 7, of the by-laws

Marchand, Jean (Essex South), 210 Lafayette Street, Salem

Shpiner, Leonard (Middlesex South), 509 Arcade Building, Kankakee, Illinois

Snow, Robert (Middlesex East), 1146 Gilmer Drive, Salt Lake City, Utah

That the following named fellow be allowed to change his legal residence from one district society to another, without change of district membership, under the provisions of Chapter III, Section 3, of the by-laws

Heusner, A Price (Suffolk), 647 Pleasant Street, East Weymouth

MICHAEL A. TIGHE, *Secretary*

EATH

HOWARD — Pérez B. Howard, M.D., of Newtonville, died January 18. He was in his seventy-first year. Dr. Howard received his degree from Harvard Medical School in 1902. He was a fellow of the American Medical Association.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

REVIEW OF COMMUNICABLE DISEASES IN 1946

More than 100,000 cases of communicable disease were reported in Massachusetts during 1946, exceeding the 1945 total by 20,000 cases. The increase was due mostly to the record-breaking number of measles cases that occurred in the spring, complemented by increases in German measles, chicken pox and dog bite. No serious outbreaks of devastating diseases took place during the year, however, and on the whole the experience with communicable disease can be considered as extremely satisfactory.

The Commonwealth was fortunate to escape with only 377 cases of poliomyelitis during an epidemic year that proved to be the greatest the Nation has experienced since 1916, when a total of 1927 cases, with 452 deaths, occurred in Massachusetts. The most alarming development of the past year was the marked increase in diphtheria, which began in July and culminated in a total of 441 cases, more than doubling the incidence for any year since 1937. This strongly indicates the immediate need of intensifying immunization efforts, especially in Boston, Gloucester, Lowell, Lynn, New Bedford, Somerville, Taunton and Worcester, where the disease has been frequent.

The prevalences of other communicable diseases did not show impressive changes during the year. Slight to moderate increases were reported in Salmonella infections, trichinosis, pulmonary tuberculosis and typhoid fever. On the other hand,

sharp decreases occurred in the incidences of scarlet fever, mumps and lobar pneumonia. A decline also was reported in bacillary dysentery, meningococcal meningitis and whooping cough.

Lobar pneumonia broke last year's all-time low to reach the lowest incidence in the history of the Commonwealth, with a total of 1484 cases, compared with 2137 in 1945. No cases of smallpox, leprosy or human rabies were reported.

Following is a list of the communicable-disease totals reported in Massachusetts during 1945 and 1946, together with the seven-year medians

DISEASE	1946	1945	SEVEN YEAR MEDIAN
Actinomycosis	-	2	4
Anterior poliomyelitis	379	527	182
Anthrax	2	4	5
Chancroid	19	20	2
Chicken pox	11506	10401	11808
Diphtheria	441	194	154
Dog bite	11705	10585	10585
Dysentery, amebic	4	18	3
Dysentery, bacillary	68	245	303
Encephalitis infectiosa	8	18	21
German measles	4610	1308	1938
Gonorrhea	5062	5487	4652
Granuloma inguinale	4	4	1
Hookworm	3	8	0
Infectious diseases of eye			
Ophthalmia neonatorum	484*	495*	675*
Trachoma	2	1	11
Leprosy	0	0	0
Lymphocytic choriomeningitis	4	8	3†
Lymphogranuloma venereum	10	31	1
Malaria	497	1031	18
Measles	28402	7486	22338
Meningitis meningococcal	121	161	161
Meningitis, Pfeiffer bacillus	30	32	20
Meningitis pneumococcal	44	42	52†
Meningitis staphylococcal strepto-			
coccal and other forms	19	25	26†
Meningitis, undetermined	42	41	74†
Mumps	5811	15727	10491
Pneumonia, lobar	1484	2137	3250
Psittacosis	2	0	0
Rabies (in animals)	2	0	0
Rabies (in human beings)	0	0	0
Rocky Mountain spotted fever	1	1	0
Salmonella infections	179	124	109
Scarlet fever	6080	10373	10373
Septic sore throat	178	200	177
Smallpox	0	0	0
Syphilis	4970	4378	5024
Tetanus	12	12	17
Trichinosis	38	28	28
Tuberculosis pulmonary	2902	2675	2816
Tuberculosis other forms	185	164	221
Tuberculosis hilum	10	14	
Tularemia	2	0	1
Typhoid fever	11	18	50
Typhus fever	3	0	2
Udulant fever	52	49	46
Wet's disease	0	3	2†
Whooping cough	6514	7445	7548

*Includes suppurative conjunctivitis.

†Four-year median.

‡Made reportable December 14, 1947

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

CLINIC	DATE	CLINIC CONSULTANT
Salem	February 3	Paul W. Hugenberger
Haverhill	February 5	William T. Green
Lowell	February 7	Albert H. Brewster
Greenfield	February 10	Charles L. Sturdevant
Gardner (Worcester subclinic)	February 11	John W. O'Meara
Brockton	February 13	George W. Van Gorder
Springfield	February 18	Garry deN. Hough, Jr.
Pittsfield	February 19	Frank A. Slowick
Worcester	February 21	John W. O'Meara
Fall River	February 24	David S. Grace
Hyannis	February 27	Paul L. Norton

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments.

MISCELLANY

NOTE

The following appointments to the teaching staff of Harvard Medical School were recently announced: Donald Robert Wilson, of Quebec, Canada (B A Oxford University, England, 1937, M D, C M University of Alberta 1931-35), research fellow in medicine, Jacques Antoine Carloti, of Paris, France (M D University of Paris 1940), research fellow in medicine, Wade Volwiler, of Athens, Ohio (A B Oberlin College 1939, M D Harvard University 1943), assistant in medicine, Louis Anthony Sieracki, of Norwood (S B University of Indiana 1927, M D University of Indiana 1929), instructor in pediatrics, Bertram Silverstone, of Norfolk, Virginia (A B Columbia University 1937, M D Harvard University 1941), assistant in surgery, Frederic Crosby Bartter, of Boston (A B Harvard University 1935, M D Harvard University 1940), research fellow in medicine, Thomas Lanier DeLorme, of Randolph (S B Howard College, Alabama, 1939, M D New York University 1943), research fellow in neurology, Gardner Cowles Quarton, of Cedar Rapids, Iowa (S B Harvard University 1940, M D Harvard University 1944), assistant in neurology, Gustave Derouaux, of Liège, Belgium (M D University of Liège 1938), research fellow in physical chemistry, Constance Elaine Field, of London, England (M R C S, L R C P, B M, B S London 1934, M D London 1937, M R C P 1941), research fellow in pediatrics, Theodore Dunham, Jr., of Pasadena, California (A B Harvard University 1921, M D Cornell University 1925, A M Princeton University 1926, Ph D Princeton University 1927), Henry E Warren Fellow in Surgery, Martin Bernard Williamson, of Las Vegas, New Mexico (S B Brooklyn College 1938, A M University of Missouri 1940, Ph D University of Missouri 1943), instructor in ophthalmic research, Sidney Bennett Luna, of Waterbury, Connecticut (S B Middlebury College, 1938, M D Harvard University 1943), assistant in surgery, Ralph Henderson Kellogg, of Saratoga Springs, New York (A B University of Rochester 1940, M D University of Rochester 1943), teaching fellow in physiology, Somers Hayes Sturgis, of Cambridge (A B Harvard University 1927, M D Harvard University 1931), assistant in gynecology, Arthur Stanwood Pier, Jr., of Milton (A B Harvard University 1935, M D Harvard University 1939), assistant in medicine, Beverly Todd Towery, of Bowling Green, Kentucky (S B Western State Teachers College, 1936, M D Vanderbilt University 1940), research fellow in medicine, and John Bruton Scanbury of Mendota, Illinois (A B Duke University 1935, M D Harvard University 1939), research fellow in pharmacology.

The appointment of Paul Hathaway Keyes, of Long Island, New York (D D S University of Pennsylvania 1941, A B University of Rochester 1945, M S University of Rochester 1947), as research fellow in dental medicine, was also announced recently.

CORRESPONDENCE

TRYPTOPHANE AND BLOOD SUGAR LEVELS

To the Editor: As an incident to the experimental ingestion of crystalline *D*-L-tryptophane, it was observed that on ingestion of this essential amino acid, there was, for the persons concerned, a slight but consistent drop in the blood sugar level. Before beginning ingestions on a large scale in an attempt to decrease the caries rate, a small group of young adults volunteered to undergo an experiment to test the blood sugar drop. A dose of tryptophane varying from 0.14 to 0.32 gm., being adjusted to body weight, was ingested by these subjects on four successive days. Then, after a day's rest, the same dose of tryptophane was ingested on four more successive days. The material was taken midway between breakfast and lunch, in crystalline powder form, with as much water as desired. Previous ingestions in gelatin capsules had proved less effective in changing the salivary amylase. All blood samples were taken after a five-hour fast, and the last dose of tryptophane was administered two hours prior to drawing the second samples.

The changes in fasting blood sugar levels following these ingestions are listed below and appear to be significant.

SUBJECT	BLOOD SUGAR	
	BEFORE TRYPTOPHANE	AFTER TRYPTOPHANE
	mg./100 cc.	mg./100 cc.
R C	91	71
G M	75	67
P H	87	89
N T	113	63
L W	87	71
B V	96	64
S T	106	88
N B	101	66
O F	101	67

Among the nine subjects, only one failed to show a decrease in the blood sugar level, and in this instance the level increased from 87 to 89 mg per 100 cc. For the other eight, the average fasting blood sugar was 96 mg (range, 75 to 113 mg) per 100 cc., and that after the tryptophane was 70 mg (range, 63 to 88 mg). This average drop of 26 mg may be of interest in diabetes and possibly in hypoglycemia. In control subjects, from whom blood samples were obtained at the same time as those from the test subjects, there was an average gain in the blood sugar level of 3 mg per 100 cc.

NAOMI COCKE TUSTIN
GEORGE EDWARD CROWELL

Forsyth Dental Infirmary
140 Fenway
Boston 15

BOOK REVIEWS

Pulmonary Edema and Inflammation. An analysis of processes involved in the formation and removal of pulmonary transudates and exudates. By Cecil K. Drinker, M.D., D.Sc. 84, chb, 106 pp., with 27 illustrations. Cambridge Harvard University Press, 1945. \$2.50.

This monograph is divided into five chapters. The first, a discussion of the anatomy of the lungs as related to the problem of transudation, includes a great deal of information that is of clinical significance — notably, a reminder that the lung capillary endothelium depends for its oxygen on air reaching it rather than on arterial blood and that exudates or transudates in this area must largely be removed through the bottleneck of the lymphatic ducts.

The second chapter discusses the balance of forces that regulate the movement of fluids through the walls of capillaries. A contrast is made between the capillary situation within the lungs and elsewhere in the body, and evidence is presented that the lung is a relatively ineffective organ for ridding itself of excessive transudation, besides anatomical peculiarities, it suffers the handicap of contending against a variable degree of negative pressure within the thorax that acts toward drawing fluid from the pulmonary blood stream.

The third and fourth chapters discuss the treatment of pulmonary edema. There appear to be two appropriate lines of attack: the combating of anoxia and resistance to the tendency of the negative pressure normally present within the chest to increase the flow of water from the lung capillaries. For the former the proper use of oxygen appears clearly indicated, for the latter, no particularly good method is at present available.

The final chapter is concerned with artificial respiration. The author believes that too little attention has been paid to the possibly harmful effect on the lungs of methods usually employed, and he predicts future modifications that will be valuable.

This book contains much more than an original discussion of applied physiology. It is prepared by a talented author who is also an artistic teacher, each chapter is readable, demonstrates on almost every page both scholarship and the writer's familiarity with every stone of the structure to which he has built his views. On the whole, the work does serve high praise, it is not only valuable for reference but also a delightful model for those interested in the art of medical writing.

Pharmacy Fundamental principles and practices, pharmaceutical preparations, biologicals Editor-in-chief, Rufus Lyman, M.D. 4th, cloth, 540 pp., with 197 illustrations Philadelphia J B Lippincott Company, 1945 \$8 00

Lyman and his group of twenty-two collaborators have used an up-to-date authoritative treatise covering the field of pharmacy in a comprehensive manner. The book represents a new trend in textbook construction in pharmacy and has been designed as a teaching textbook and a reference for the practicing pharmacist as a working tool. The authors are specialists in their various fields. The work is divided into three parts. The first part deals with the fundamental principles of the basic sciences as applied to pharmaceutical processes, the second covers the field of pharmaceutical preparations, with emphasis on the processes involved in manufacture, and the third discusses products of biologic origin (the vitamins, hormones and endocrine preparations). The text is well written and printed in two columns with good type on good paper. The book is recommended for medical libraries and should prove valuable as a reference source for all public libraries.

Way of an Investigator A scientist's experiences in medical research By Walter B Cannon, M.D. 8th, cloth, 229 pp. New York W W Norton and Company, Incorporated, 1945 00

The late Dr. Cannon, in this delightful semiautobiography, based on more than forty years of his life spent in the Harvard Medical School, expounds the philosophy of the scientific investigator. He discusses the qualifications of the ideal scientific worker, the necessity of perseverance and stamina, the intuition and accident play in discovery and the problems that arise from the possible errors and misjudgments that are bound to occur in research. Professor Cannon tells of his early home and college life, his travels abroad, his war experiences, his vacations and his years as professor of physiology. The text is written in an easy, interesting style, and this book is worthy of a place in all libraries, medical, scientific in general, and in all private medical collections.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return or the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Master-of-Paris Technique in the Treatment of Fractures and Other Injuries By Lieutenant Colonel T B Quigley, Medical Corps, Army of the United States, instructor in surgery (on leave of absence), Harvard Medical School, and junior associate in surgery (on leave of absence), Peter Bent Brigham Hospital, Boston. 8th, cloth, 107 pp., with 103 illustrations. New York The Macmillan Company, 1945 \$3 50

This manual considers only the mechanical application with one method of treatment of traumatic injuries and only brief mention of the common indications for each cast is made. The diagnosis, evaluation, pathology and prognosis of trauma are not considered. The majority of casts used in ordinary practice are described.

Hematology By Willis M. Fowler, M.D., professor of internal medicine, University of Iowa. With a chapter by Elmer L. Degowin, M.D., assistant professor of internal medicine, University of Iowa. 8th, cloth, 409 pp., with 110 illustrations. New York Paul B Hoeber, Incorporated, 1945 \$8 00

This new textbook on hematology, which was developed by the author from his lecture notes covering the period of the last twelve years, was written primarily for the medical student and the general practitioner, not being designed to serve as a general reference work for those specializing in hematology. The author maintains the viewpoint that hematology is a part of internal medicine rather than a specialty in itself and presents the subject in this light, stressing the clinical and therapeutic aspects of the various diseases. The book is well printed on good paper, with a good type, but is rather heavy for its size.

Clinical Atlas of Blood Diseases By A Piney, M.D., M.R.C.P. physician, St. Mary's Hospital for Women and Children, London, and Stanley Wyard, M.D., F.R.C.P., physician, Royal Cancer Hospital, and Princess Beatrice Hospital, London. Sixth edition. 8th, cloth, 137 pp., with 48 illustrations. Philadelphia The Blakiston Company, 1945 \$5 00

The value of this small atlas is demonstrated by the need of six editions during a period of fifteen years. The book is primarily an atlas, but condensed descriptions of blood conditions accompany the plates.

Amputation Prosthesis Anatomic and physiologic considerations, with principles of alignment and fitting designed for the surgeon and limb manufacturer By Atha Thomas, M.D., associate professor of surgery (orthopedics) University of Colorado School of Medicine, and Chester C Haddan, president, Association of Limb Manufacturers of America. 8th, cloth, 350 pp., with 207 illustrations. Philadelphia J B Lippincott Company, 1945 \$8 00

In this monograph, written jointly by a surgeon and a manufacturer of artificial limbs, the problems of the patient, the surgeon and the appliance maker are discussed on common ground and emphasis is placed on the most satisfactory end results for the patient. The importance of anatomic and physiologic considerations in doing an amputation is stressed in relation to established principles of alignment and fitting. The book is designed as a practical guide for the proper use of prosthetic appliances. This unusual book should be in all medical libraries.

Structure and Function of the Human Body By Ralph N. Baillif, Ph.D., assistant professor of anatomy, Louisiana State University School of Medicine, New Orleans, and Donald L. Kimmel, Ph.D., associate professor of anatomy, Temple University School of Medicine, Philadelphia. 8th, cloth, 328 pp., with 158 illustrations. Philadelphia J. B. Lippincott Company, 1945 \$3 00

The objective of this new manual is to provide a carefully organized text emphasizing the relation of structure and function. The manual, which is written primarily for students, emphasizes the unity of structure and function. The material is well organized and well printed, with a good type, and should prove valuable to all those who have need of such a manual. A special glossary is appended to the text.

Analyze Yourself Enabling anyone to become deeply psychoanalyzed without a personal analyst By E. Pickworth Farrow, M.A., D.Sc. With a foreword by the late Professor Sigmund Freud, M.D., LL.D. New York International Universities Press, 1945 \$2 00

This small book contains a full and detailed account of how to follow a practical method of psychoanalysis of one's own mind. The author used the method on himself and relates his own experiences in recapturing his memory extending over a period of years.

An Introduction to Physical Anthropology By M. F. Ashley Montagu, B.S., Ph.D., associate professor of anatomy, Hahnemann Medical College and Hospital, Philadelphia, and visiting lecturer, Department of Sociology, Harvard University. 8th, cloth, 325 pp., with 25 illustrations. Springfield, Illinois Charles C Thomas, 1945 \$4 00

This manual has been written for the general reader and the student, and it is hoped that it will prove of value to biologists, physicians and psychologists. The author has endeavored to present the fundamental facts and problems necessary for the understanding of man. He discusses in order the primates as a zoological group, the origin and evolution of the primates and of man, the criteria and mechanism of ethnic group differentiation, the divisions and ethnic groups of man, the relation between body, mind and culture, heredity and the influence that the environment has on man. An appendix comprises a practical synopsis of methods of measurement in physical anthropology. In addition to lists of references for further reading appended to each chapter, a general bibliography concludes the volume. The text is easy to read, and the book is printed with a good large type, on good paper. This introduction should prove valuable to all those desiring a short text on the subject.

NOTICES

ANNOUNCEMENTS

Dr Archie A Abrams calls attention to the omission of his office address and telephone number from the current telephone directory. His office is at 1093 Beacon Street, Brookline, and the telephone number is ASPinwall 8951

Dr Volta R Hall announces the opening of his office for the practice of psychiatry at 372 Marlborough Street, Boston

Dr Merrill Moore has returned from military service and announces the opening of his office at 433 Marlborough Street, Boston. His telephone number is COMMONwealth 4216

Dr Bernard J Niemiro, of 207 Elm Street, Holyoke, announces that in the future his practice will be limited to proctology

Dr Robert R Shapiro announces the removal of his office for the practice of general surgery and of surgery of the sympathetic nervous system from 319 Longwood Avenue to 31 Bay State Road, Boston

JOSEPH H PRATT
DIAGNOSTIC HOSPITAL

Bennet Street, Boston

Lecture Hall, 9-10 a m

MEDICAL CONFERENCE PROGRAM

Wednesday, February 5 — The Use of Isopropyl-amine-ethanol in the Management of Bronchial Asthma Dr Maurice S Segal

Friday, February 7 — Diseases of the Veins in Older Patients Dr Edward A Edwards

Wednesday, February 12 — Incomplete and Complete Lacerations of the Perineum Their surgical management Dr Louis E Phaneuf

Friday, February 14 — Clinicopathological Conference Drs Chester S Keefer and H E MacMahon

Wednesday, February 19 — Pediatric Clinicopathological Conference Drs James M Baty and H E MacMahon

Friday, February 21 — The Mechanism of Hemoglobinuria in Thermal Burns Dr Thomas Hale Ham

Wednesday, February 26 — The Use of Streptomycin in Tuberculosis Dr Lowrey F Davenport

Friday, February 28 — Intracranial Aneurysms Dr William H Sweet

On Tuesday and Thursday mornings, Dr S J Thannhauser will give medical clinics on hospital cases. On Saturday mornings, clinics will be given by Dr William Dameshek. Medical rounds are conducted each weekday by members of the staff from 12 00 to 1 00 in the Lecture Hall. All exercises are open to the medical profession

NEW ENGLAND DERMATOLOGICAL SOCIETY

The regular meeting of the New England Dermatological Society will be held in the Skin Out Patient Department of the Massachusetts General Hospital on Wednesday, February 12, at 2 00 p m

TUFTS ALPHA OMEGA ALPHA

The Tufts chapter of the Alpha Omega Alpha will meet in the auditorium of the Beth Israel Hospital, Boston, on Wednesday, February 5, at 8 30 p m. Dr Erich Lindemann will speak on the subject "Some Psychological Problems in Medicine"

APPOINTMENT OF U S P H S MEDICAL OFFICERS

A competitive examination for appointment in the Regular Corps in the grades of assistant surgeon (first lieutenant) and senior assistant surgeon (captain) will be held in the near future

Regular Corps appointments are permanent in nature and provide opportunities to qualified doctors for a life career in one or more of a large number of fields, including research, general hospitals, special hospitals, foreign duty and federal, state and local public-health programs. Assignments are made with all possible consideration of the officer's demonstrated abilities and experience. There is ample opportunity for professional growth and development

All applicants must be at least twenty-one years of age, must be citizens of the United States, must present a diploma of graduation from a recognized medical school and must satisfactorily pass a physical examination performed by Public Health Service officers when directed upon successful completion of the oral and written examination

Applicants for the grade of assistant surgeon must have had at least seven years of educational and professional training or experience exclusive of high school. Applicants for the grade of senior assistant surgeon must have had at least eleven years of educational and professional training or experience exclusive of high school

Application forms may be obtained by writing to the Surgeon General, United States Public Health Service, Washington 25, D C. These should be retained and presented to the Board at the time the applicant appears for the oral examination

Entrance pay for assistant surgeon with dependents is \$3811 a year, and for senior assistant surgeon with dependents is \$4351 a year. Promotions are at regular intervals up to and including the grade of medical director, which corresponds to full colonel at \$8551 a year. Retirement pay at sixty-four is \$4950 a year. Full medical care, including disability retirement at three-fourths pay, is provided. All expenses of official travel are paid by the Government. Thirty days' annual leave with pay is provided

Examinations will be oral and written. The oral examination will be held at several places throughout the country; in the New England area it will start at 10 00 a m on March 4 at the Marine Hospital, 77 Warren Street, Brighton, Boston. The written examination will be held at 9 00 a m on March 27 and 28 at places convenient to the candidates and the Service. National Board grades may be used in place of the written examination for the grade of assistant surgeon

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 6

FRIDAY, FEBRUARY 7

*9 00-10 00 a m Diseases of the Veins in Older Patients Dr Edward A Edwards Joseph H Pratt Diagnostic Hospital
*10 00 a m-12 00 m Medical Staff Rounds Peter Bent Brigham Hospital

MONDAY, FEBRUARY 10

*12 15-1 15 p m Clinicopathological Conference Peter Bent Brigham Hospital

TUESDAY, FEBRUARY 11

*12 15-1 15 p m Clinicorontogenological Conference. Peter Bent Brigham Hospital
*8 00 p m Harvard Medical Society Amphitheater, Peter Bent Brigham Hospital

WEDNESDAY, FEBRUARY 12

*9 00-10 00 a m Incomplete and Complete Lacerations of the Perineum Their surgical management Dr Louis E Phaneuf Joseph H Pratt Diagnostic Hospital
*11 00 a m-12 00 m Medical Clinic Amphitheater Children's Hospital

*12 00 m Clinicopathological Conference (Children's Hospital) Amphitheater, Peter Bent Brigham Hospital
2 00 p m New England Dermatological Society Skin Out Patient Department Massachusetts General Hospital

*2 00-3 00 p m Combined Clinic by the Medical, Surgical and Orthopedic Services Amphitheater Children's Hospital

*7 15 p m Graduate Seminar in Pediatrics Children's Medical Service Amphitheater 3A Massachusetts General Hospital

*Open to the medical profession

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The New England Journal of Medicine

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Volume 236

FEBRUARY 6, 1947

Number 6

THE ROLE OF THE SURGEON IN THE MANAGEMENT OF PEPTIC ULCER*

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ULCER is a more frequent cause of discomfort and disability than of death—that is, for every patient who dies, a far larger number suffer. Yet approximately 10,000 people die annually in the United States from ulcer and its complications. There has been no suggestion of improvement in this mortality, such as that in appendicitis and bowel obstruction during the past decade.

GENESIS OF ULCER

Autopsy records indicate that evidence of an ulcer or ulcer scar can be found in 2 to 5 per cent of cases. The observations of William Beaumont¹ on Alexis St. Martin and those of Wolf and Wolff² on their subject Tom suggest that gastric erosions occur readily in the stomach. Moreover the observations of Kolouch,³ of this laboratory, on the extenozed gastric or intestinal mucosal patch denote that the progress from a mucosal erosion to a fully developed ulcer can occur during the course of a few hours under the influence of dripping of gastric juice on the patch. The causal antecedent of ulcer—mucosal erosion—probably occurs not infrequently in the lives of persons who never develop an ulcer or suffer ulcer symptoms.

The latitude of difference between a patient who develops a clinical ulcer and one in whom ulcer fails to progress beyond the erosion stage is not measurable. Every person whose stomach responds normally to ingestion of food and other stimuli may be a potential ulcer candidate. Resolving the nature of the ulcer diathesis is not an easy matter.

Ulcer, which often develops spontaneously in man, is decidedly unusual in the ordinary laboratory animals, as both Mann⁴ and Ivy⁵ have been at pains to point out in observations on dogs. The standard laboratory procedure for the production of ulcer in the dog up until recently was the Mann-

Williamson⁶ procedure of moving the duodenal segment, into which bile and pancreatic juice drain, down to the terminal ileum and thus precluding opportunity for neutralization of the acid gastric juice by the alkaline digestive juices. This disarrangement of Nature's plan obviously is distinctly unphysiologic from many points of view, nevertheless, the method has been of value in focusing notice on the great importance of the acid-peptic factor in the genesis of ulcer. This laboratory has for some time been exploring agencies that abet or accelerate the ulcer diathesis. The placement of histamine in beeswax,⁷ from which vehicle the histamine is gradually released, has proved a useful tool in the investigation of items that may favorably influence the ulcer diathesis. By this means alone, ulcer can be produced in most laboratory animals.^{8,9} Moreover, agencies by which the blood supply of the gastric or duodenal mucosa may be altered or impaired appear to favor the development of ulcer. Fractures accompanied by fat embolism may give rise to the spontaneous occurrence of ulcer in man.¹⁰ Fat, injected intravenously into small laboratory animals in small doses, when accompanied by the simultaneous administration of histamine in beeswax, abets and accelerates the development of ulcer. Similarly, anoxic areas produced in the gastric mucosa by the administration of Pitressin or adrenalin favor the development of ulcer.¹⁰ Surprisingly enough nitroglycerin appears to have the same effect.

TREATMENT

The objective of treatment in conditions that threaten life or make patients miserable is to save life, allay symptoms, re-establish normal function and restore the patients to economic usefulness—by the simplest and most effective means. There are essentially three ways of treating an ulcer. In the first the physician—in this instance a psychiatrist or psychosomaticist—endeavors to talk the patient out of his difficulty. This is obviously the simplest form of therapy, but it remains to be proved, despite the present popularity of the method,

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 23, 1946.

This study is based on research supported by grants from the Graduate School, the John and Mary R. Markle Foundation and the Augustus L. Searle Fund for Surgical Research.

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¹Ch. of Department of Surgery, University of Minnesota Medical School.

how permanent the results of such treatment may be. Secondly, the patient is instructed to eat his way out of his troubles — diet. And thirdly, surgery is invoked with the hope that this expedient will ensure a more lasting cure than that achieved by the two preceding agencies.

As a surgeon, it would be presumptuous of me to attempt to discuss any but the last aspect of this problem.

Indications for Operation

In our clinic, 80 per cent of patients undergoing resection for ulcer have had one or more of the conventional complications of ulcer, including perforation, hemorrhage and obstruction. In our experience, the typical patient accepting resection for ulcer is a man in the middle forties whose symptoms trace back fifteen years. Inasmuch as the patients come largely from the rural areas of Minnesota, the typical patient is a farmer whose work should not be especially conducive to the ulcer diathesis. Moreover, I have been unable to observe in these patients any common behavior pattern, which the routine employment of psychiatric technics might uncover, nor can I see any such uniform physical conformation in ulcer patients as was formerly described under the designation "ulcer habitus."

In this clinic, only 2 patients under twenty years of age have undergone resection for ulcer. One was a boy of fourteen who first suffered a severe hemorrhage from a duodenal ulcer at the age of ten. After an interval of four years, during which many such occurrences threatened his life, a three-quarter resection was undertaken in the presence of massive hemorrhage. More than six years have elapsed, and the boy has grown to manhood. There has been no suggestion of recurrence. The other patient was a nineteen-year-old boy with repeated massive hemorrhages from a duodenal ulcer. He too has remained well.

Approximately a dozen patients in their twenties have been subjected to resection for ulcer. Patients in their thirties are more numerous, and a fairly large number first developed symptoms in the sixth or seventh decade of life. Several patients in their eighties have submitted to resection for ulcer because of compelling indications for operation, or because of long continued dissatisfaction with medical management.

Perforation There can be no disagreement concerning the manner of treatment of perforation. This complication has been an important element in the mortality of ulcer. Yet considerable improvement has resulted from the following methods of dealing with perforated ulcers: the use of unabsorbable (silk) sutures, employing Graham's¹¹ technic of placement of the sutures, lavage of the peritoneal cavity with copious quantities of physiologic saline solution, and the use of chemotherapy. Whereas the general mortality from acute perfora-

tion still hovers around 20 to 25 per cent, in institutions where the above precepts guide the therapy, the mortality is approximately 5 per cent.

Hemorrhage There is room for considerable improvement in the management of hemorrhage attending ulcer. Allen and Benedict¹² were responsible for persuading American surgeons to operate in an attempt to save the lives of patients suffering from massive hemorrhage. The difficulties relative to the problem are many. The decision whether operation should be undertaken is not easily made. Often, too much time is lost by attempts to replace blood loss that is continuing. When a patient has repeatedly been in shock, he is not a good candidate for operation. Physicians and surgeons would do well to consider operating immediately on patients who have a long history of ulcer with previous hemorrhages. The problem may be difficult on other scores. The diagnosis may be in doubt. Gastric cancer, in the experience of our clinic, is not an infrequent cause of sudden massive hemorrhage. And the technical problem in a duodenal ulcer with a large crater may be extremely difficult. The situation usually demands that the duodenum be cut across to find and arrest the source of hemorrhage, then, there remains the extremely difficult task of obtaining a satisfactory closure of the open duodenum — a problem that may be perplexing especially in the large supraduodenal ulcer crater with perforation into the hepatoduodenal ligament. A number of studies suggest that the mortality in patients treated medically for massive hemorrhage is in the neighborhood of 10 to 13 per cent.¹³ Early resort to surgery will spare the lives of many such patients who will otherwise die from exsanguination. In the patient who presents both obstruction and massive hemorrhage, the indication for early surgery is especially imperative.

In this connection, it is probably not out of place to indicate that, in certain cases, the cause of the bleeding remains occult at operation. On the thesis that such bleeding comes usually from a small mucosal erosion that cannot be felt through the gastric wall, I have resected a number of stomachs for massive hemorrhage. Several of these case histories have been reported in detail elsewhere.¹⁴ The situation of fatal bleeding from a single small mucosal erosion in the stomach is well known to pathologists. The condition may be passed over by the surgeon at operation. In cases of massive loss of blood by vomiting, when the surgeon fails to find a likely source for the difficulty, the possibility of a superficial gastric erosion should not be overlooked.

Moreover, bleeding in portal hypertension may also be amenable to correction by gastric resection. It has been taught that the chief source of bleeding is ruptured esophageal varices. Inasmuch as obstruction of the superior vena cava may also give rise to esophageal varices unaccompanied by hemor-

e, may it not be proper to ask whether the ulcer process is due to acid and peptic erosion rather than to hydrostatic rupture? Already, it has been shown that portal hypertension abets the ulcer process.¹⁰ Furthermore, whereas a three-quarter gastric resection uniformly protects against the amine-provoked ulcer in the dog, a 90 per cent resection fails to afford consistent protection against an ulcer in the presence of portal hypertension. Obviously, the intent of gastric resection for hemorrhage in the presence of cirrhosis or thrombophlebitis of the portal or splenic vein, or both, is to prevent death from bleeding and thus to prolong life.

The operation does not do away with portal hypertension. An operation approaching a total gastrectomy will, I believe, protect against hemorrhage. If the bleeding is occurring from gastric or duodenal erosion, the operation should be adequate. If esophageal erosions are responsible, the separation of the esophagus from the portal circulation will relieve the esophageal veins from the increased portal pressure. Moreover, reduction of gastric acidity will diminish the tendency to acid-peptic erosion and the esophageal varices.

Obstruction The most frequent cause of pyloric obstruction is an occult, sealed ulcer crater with extension into the surrounding tissues — that is, the area of induration accompanying a perforating ulcer. A perforated ulcer in juxtaposition to the pylorus suggests about extrinsic duodenal compression and obstruction. The usual location of such an ulcer crater is the posterior wall, with penetration of the pancreas, often, the perforation is into the hepatoduodenal ligament at the superior border of the duodenum. In my experience, the latter circumstance as a cause of obstruction is far more frequent than intrinsic duodenal stenosis. Spasm and mucosal edema, incident to an ulcer near the pylorus, are phenomena that may cause obstructive symptoms. Persistent or recurrent pyloric obstruction generally occurs through Nature's attempt to halt the extension of the ulcer crater. The repair phenomenon of cicatricial contraction is greater in a penetrated ulcer that has extended through all the coats of the gastric or duodenal wall than in an ulcer that has not penetrated through all the layers of the bowel wall. Patients whose obstruction remains refractory to conservative treatment must be operated on.

Pain In approximately 20 per cent of patients subjected to gastric resection in our clinic, the major consideration that prompted performance of the operation was failure to control pain satisfactorily by dietary measures. Occasionally, a patient's own dissatisfaction with the dietary strictures, whether arising from a dislike of the monotony of the diet or from inability to work under its conditions, has constituted the main indication for operation.

DISSATISFACTION WITH MEDICAL CURE

Dr John Fast¹⁴ has just completed a study in our laboratory that strongly suggests the efficacy of the Sippy diet in ulcer management. Five dogs were given 30 mg of histamine in beeswax daily over a forty-day interval. Meanwhile they were fed the Sippy regimen by a gastrostomy tube from 7 a m to 9 p m. At post-mortem examination, ulcer was not observed in a single animal. The only other measure observed that will protect uniformly against the histamine-provoked ulcer is a three-quarter gastric resection.

In most cases dieting for ulcer is not unlike taking insulin for diabetes. It works so long as the medicine is taken. One of the difficulties, however, is that the gastric mucosa is a sympathetic tissue and responds to diverse stimuli of every sort. Almost anything ingested stimulates gastric secretion. Protein-containing foods possess the greatest capacity of uniting with the hydrochloric acid of the gastric juice, and amino acids appear to be more effective in this respect than native proteins. We have found no substrate, however, that, when fed through an indwelling gastric tube, keeps the reaction of the gastric juice in patients with bleeding ulcer consistently above pH 3.5 — the proteolytic end point for pepsin. Arrest of the acid-peptic erosive action of the gastric juice by any agency would be a great boon in the treatment of ulcer, particularly in the management of actively bleeding ulcers.

Nevertheless, dissatisfaction with the dietary management of ulcer is being forcefully expressed. Heuer, Holman and Cooper¹⁵ have reviewed the results of medical and surgical treatment of ulcer at the New York Hospital. They found that approximately 40 per cent of patients have unsatisfactory results from medical treatment. More recently, Krarup¹⁶ reviewed the results of medical treatment of ulcer on Meulengracht's service at the Bispebjerg Hospital in Copenhagen. He observed that the results of treatment were poor in 24 per cent of bleeding and in 43 per cent of nonbleeding ulcers. In patients in whom the duration of ulcer symptoms was longer than a year prior to treatment, the incidence of failure of medical treatment was 32 per cent in bleeding and 45 per cent in nonbleeding ulcers. In patients who had previously undergone one or more medical regimes for ulcer, the incidence of failure was 34 per cent for bleeding and 58 per cent for nonbleeding ulcers. Krarup concluded that in patients whose ulcer distress is of more than a year's duration, and if two medical regimes have been gone through without recovery, the chance of failure of repeated medical treatment is so great that surgical treatment ought to be taken into consideration.

A deterrent, to which careful heed should be given in the protracted conservative management

how permanent the results of such treatment may be. Secondly, the patient is instructed to eat his way out of his troubles — diet. And thirdly, surgery is invoked with the hope that this expedient will ensure a more lasting cure than that achieved by the two preceding agencies.

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patient. At the time of the first gastric resection only a small section of stomach (155 gm), including 6 cm of jejunum, which was not weighed separately, was removed, if this segment is considered to have weighed 20 gm, a section of stomach weighing only 135 gm was removed — too small an amount for the usual resection. The primary difficulty is, however, that stout men of hypersthenic build have a short transverse stomach whose fundus closely tethered to the left diaphragm and the spleen. In other words, in a thin patient whose stomach hangs down in the form of a fishhook, it is not a difficult task for the surgeon to remove the requisite amount of stomach. In an obstructed patient, the usual weight of the excised gastric tissue in a three-quarter resection is 150 gm. In patients with obstruction the weights of such excised specimens obviously run considerably higher. In the patient with the recurrent stomal ulcer on whom I reoperated, an additional 86 gm of gastric tissue was removed. He has remained well.

The policy in our clinic has been to do a one-stage procedure, taking time to do what needs to be done. There is little justification for performing an inadequate operation such as gastrojejunostomy²⁰ in the difficult cases, electing to perform gastric resection only in those patients in whom it may be performed without difficulty. Moreover, in difficult duodenal ulcers a choice need not lie between a compromise measure, such as gastrojejunostomy with an admitted incidence of stomal ulcer of 15 per cent, and a resection that risks the continuity of the common bile duct and requires a tube in the duct.²¹ The antral mucosa can be excised, the pyloroantral muscle cylinder being left. The experience of our clinic is that such an operation can be done with a reasonable risk, and the ultimate promise of success is the same as in the straightforward gastric resection.²² As a matter of fact, in these difficult operations, performed on somewhat less than 100 patients, there have been no stomal ulcers. The objection to more universal adoption of the pyloric exclusion operation, with excision of the antral mucosa, has been fear of leakage through the segment with the development of a subphrenic abscess.

THE DUMPING SYNDROME

One of the disturbing items accompanying gastric resection has been the occurrence in some patients of what might be described as the "dumping syndrome," which is frequently observed in all patients soon after operation but persists in a few or long periods. Whether these symptoms are physiologic or psychologic is difficult to determine. Dr David Gaviser²³ has been at work in this clinic on the problem for some time, and it is hoped that some enlightenment may be shed on its mechanism. Loss of the pyloric sphincter in gastric resection permits quick filling of the jejunal segment, a cir-

cumstance against which the pylorus ordinarily affords protection. Sudden dumping of the contents of the stomach into the jejunum may be accompanied by nausea, pain and vomiting. Eating slowly and in small amounts at a time, and the avoidance of drinking with meals, ameliorates the symptoms considerably. In most cases the time factor adjusts the situation satisfactorily. The frequency with which milk and cream are shunned by the ulcer patient after gastric resection suggests that the problem merits investigation.

Moreover, some patients undergoing gastric resection for ulcer, particularly those who were thin prior to operation, manifest some difficulty in maintaining weight. Whether this circumstance is due to difficulty with food ingestion or to absorption is not known. Metabolic studies should be made in a few such patients to determine whether the operation has interfered with the assimilation of protein and fat.* Serious anemia has not been observed after the three-quarter resection for ulcer.

* * *

It is not known whether the margin of difference between a patient having an ulcer and another without ulcer, whose stomach responds normally to extrinsic stimuli, is wide or narrow. No means of measuring this difference have been determined. Whether the difference is qualitative or quantitative and primarily concerns factors of secretion or tissue resistance to acid-peptic erosion is also not known. I am inclined to believe that the latitude of difference between a patient with ulcer and another without ulcer is not great. In other words, patients whose stomachs secrete normally may be tight-rope walkers so far as the ulcer problem is concerned and may, with slight provocation, be catapulted into ulcer difficulties. The great advantage of a slightly superior force is well documented in biology. The lungs are kept expanded by a force that is less than 1 per cent of the major operating force, atmospheric pressure.

Ulcer can be produced by stimulating an animal's endogenous gastric secretory mechanism with histamine. Moreover, agencies that favor the occurrence of anoxic areas in the gastric mucosa encourage the ulcer diathesis.

The three-quarter (75 per cent) gastric resection protects against the ulcer provoked by histamine in beeswax in the dog. Employment of a long afferent duodenojejunal loop in such an anastomosis invites stomal ulcer. Vagotomy fails to protect against the histamine-provoked ulcer in the dog, rabbit and cat. The Sippy diet fed through a gastrostomy tube to dogs receiving histamine in beeswax affords protection against the development of ulcer.

*Wallace and his associates at the Mayo Clinic have recently reported carrying out such studies (Forum on Fundamental Surgical Problems, Cleveland, December 19, 1946). They observed unusually large amounts of fat in the stools of some patients who experienced difficulty in maintaining their weight after a Billroth II type of gastric resection for ulcer.

of any patient with a persistent gastric ulcer, is that the possibility of malignancy cannot be completely excluded. In prepyloric lesions, in particular, this is an important consideration — so important, I believe, that in all patients with such defects the item of malignancy should be carefully weighed. The roentgenologist should appreciate how much the nature of his report determines or influences the course of action in such patients.

SHORTCOMINGS OF SURGERY

Dissatisfaction with the accomplishments of surgery in the ulcer problem is also real. The distrust of internists, actuaries and military authorities in the ability of surgeons to rehabilitate medical failures of ulcer management by surgical treatment is well known. Surgeons, obviously, have been too empirical in their approach to the ulcer problem, endorsing and employing procedures without a clear-cut definition of the criteria of an acceptable operation for ulcer. Let anyone who suggests a new operation for ulcer that is not founded on sound physiologic principles beware of the hazards of premature judgment! The late Lord Moynihan stated that the accomplishments of gastrojejunostomy stamped it as one of the great operations devised by surgeons for the relief of ulcer. What empty words in the light of critical experience!

AN ACCEPTABLE OPERATIVE PROCEDURE

The histamine-in-beeswax technic has proved a useful instrument in defining the criteria of an acceptable operation for ulcer. A three-quarter (75 per cent) gastric resection made with a short afferent duodenal loop affords consistent protection against the histamine-provoked ulcer in dogs when other abetting influences are not employed simultaneously. Gastrojejunostomy and the small gastric resection (less than 50 per cent) fail consistently. The experimental evidence of the necessity of employing a short afferent duodenojejunal loop to protect against recurrent ulcer appears complete. The Billroth I procedure apparently necessitates the same extent of resection (75 per cent) as a satisfactorily performed Billroth II operation to protect against the histamine-provoked ulcer.¹⁰ In man, excision of the antral mucosa is a necessity, failure to remove the mucosa, even despite an otherwise adequate gastric resection, invites a stomal ulcer. Vagotomy also fails to protect against the histamine-provoked ulcer. Inasmuch as histamine acts directly on the parietal cells in the gastric tubules, no such protective action of histamine from vagotomy is perhaps to be anticipated. Hartzell¹⁷ studied the effect of bilateral vagotomy on gastric secretion in the dog. During the five-month interval following operation, Hartzell noted a distinct reduction in the gastric secretory response to ingested meat. Vanzant¹⁸ restudied the remote results of vagotomy in 4 of Hartzell's 8 dogs more than two years after the

vagotomies had been done. At that time, Vanzant noted that the depressing effect of vagotomy on gastric secretion had been lost. The cephalic-psyche phase of gastric secretion, which is ablated by vagotomy, may be a vital factor in the spontaneous occurrence of ulcer in man. That the cephalic phase of gastric secretion may be more important in man than in the dog is difficult to believe, when one observes the eagerness of a hungry dog anticipating a piece of meat. In any event, the observations of Dragstedt¹⁹ and his associates will be followed with the keenest interest by all who are concerned with the problem. Vagotomy, however, is not an experiment that should be undertaken simultaneously in many quarters. Dragstedt will be able to determine in reasonable time whether the results in man are abiding.*

SURGICAL CURE

A successful operation for ulcer must not compromise the future for the patient by holding over him the threat of recurring ulcer. That, in the main, has been the indictment against operations for ulcer, it is a just criticism. A satisfactory operation for ulcer, in addition, in the hands of experienced surgeons, should carry a risk to life that is less than that of the disease for which operative relief is undertaken. Furthermore, it should hold out to the patient relief from distress and from the monotony of dietary strictures. An acceptable operation for ulcer should impose no significant new difficulties on the patient.

It is well known that patients with gastric ulcer are more readily cured of the ulcer diathesis by surgery than patients with duodenal ulcer. Similarly, women appear to be more easily amenable to cure by operation than men, in whom ulcer is far more frequent.

RESULTS OF OPERATION

The experience of this clinic is that gastric resection for ulcer, as described below, can be carried out in elective operations at a risk of 2 or 3 per cent. The over-all mortality, including that in emergency operations for perforation and massive hemorrhage, has been 5 per cent. In more than 500 consecutive patients who have had resections for ulcer performed over an eight-year period, there have been 2 cases of stomal ulcer, both of which occurred in heavy men, short in stature and of stocky, hypersthenic build. Both patients had undergone an earlier gastrojejunostomy for bleeding duodenal ulcer elsewhere. Both patients have severe hypertension. One of them has done well, with a partial return to some of the dietary strictures to which he submitted before operation. I have operated again on the

*In a paper presented before the St. Paul Surgical Society on January 15, 1947, by Dr. Waltman Walters and his associates of the Mayo Clinic, little support was lent to the thesis that vagotomy is a satisfactory primary operation for ulcer. They reported failure of the ulcer to heal following vagotomy as well as cases of hemorrhage and perforation. Such occurrences do not augur well for the future of vagotomy.

side or the other. Yet it may be substernal, a strong element of distress or gripping. It is less specific, perhaps, than pain and is not significant when combined with hemoptysis, which is extremely important if present, although a diagnosis is often made without it. When associated with cardiac failure, it strongly suggests embolism. Shortness of breath is associated with the severer cases of embolism, especially when there is other evidence of right-sided cardiac embarrassment. It is not although it may lead rapidly to death, its persistence for many hours or even days is not inconsistent with complete recovery. Pulmonary and peripheral congestion, as signs of cardiac failure, are frequently noted in medical cases.

Associated symptoms and signs of thrombosis in the legs are observed with a frequency proportional to the diligence with which they are sought. They are best seen against a background of preliminary routine observations and, since even a bilateral thrombosis is rarely symmetrical, by comparison of one leg with the other. Subjective complaints usually take the form of pain, referred to some part of the calf and, as a rule, accompanied by local tenderness of a deep sort, particularly on the outer anterior face of the lower leg. Objective signs of thrombosis are related to the state of the great muscles. The earliest are slight increase, by measurement, of the largest diameter of the calf, an increased firmness or elasticity on compression and a tendency to resist dorsiflexion. Signs of venous engorgement are not to be expected in bed patients at slight cyanosis of the foot may be evident on standing or even on hanging a leg out of bed and edema, on more prolonged dependency.

An elevation of the pulse rate and temperature — a clue that is especially emphasized by Bauer¹⁻³ and by Allen and his associates^{4, 5} — is most frequently obtained from a surgical chart that has previously leveled off following an operation or injury. It appears to be seen less often in patients with cardiac disorders and other serious illnesses. It may well represent early, preclinical pulmonary embolism.

Circulatory failure of some degree — that is, faintness or actual loss of consciousness — may result reflexly from any infarction. The general circulation may react rather violently to the lodgment of an embolus, and yet may readjust itself within a few hours if no further insult occurs.

Roentgenologic evidence of pulmonary infarction, if obtainable, is of primary importance, as Hampton and Castleman^{6, 7} have demonstrated. But the infarct, although entirely characteristic, if a proper exposure can be secured for the x-ray film shows poorly in plates taken in bed. It is therefore best seen in ambulatory patients deliberately studied, of course, not all emboli cause infarction, owing to the unpredictable efficiency of the collateral pulmonary circulation.

Electrocardiographic signs, which are for the expert, may be pathognomonic, especially soon after the embolus has lodged. Sometimes, exclusion of coronary thrombosis indicates an unsuspected pulmonary embolism.

With such aids to diagnosis in mind, pulmonary embolism can be identified in a surprisingly large number of cases. Undoubtedly, the profession is becoming increasingly alert to its presence. Given a suggestion that embolism has occurred, the slightest sign of thrombosis in the legs is confirmatory. But even without such confirmation, the diagnosis can be made by a study of the nature of the attack or attacks, checked by roentgenologic and cardiographic evidence. Note should, of course, be taken of fatal embolism, but nonfatal forms are more worthy of study.

PHLEBOTHROMBOSIS (QUIET THROMBOSIS) AND THROMBOPHLEBITIS

Thrombosis in the veins of the legs should not be regarded as too mysterious a disease. Unfortunately, like many other disorders, it was first recognized in its late, advanced stage — in this case, the unmistakable state of venous obstruction familiar to all as phlebitis or phlegmasia alba dolens. This outspoken state should, for the moment, be forgotten or regarded as an end-result, a thrombotic occlusion of the femoral and iliac veins. It carries a threat of many disagreeable aftereffects but little danger of embolism. It is rather on the early quiet or bland stage, from which Bauer,¹⁻³ by phlebographic studies, has proved that it develops, that one should concentrate. This Ochsner⁸ has called "phlebothrombosis."

I can do no better than quote from an address of Dr. Lewis A. Conner,⁹ in which he recalls his experiences of many years ago with the thrombophlebitis of typhoid fever:

It was found that, by careful daily examinations of the lower extremities of every typhoid patient throughout the course of the disease, it was possible to recognize a beginning thrombosis, often many days before the classic symptoms of femoral thrombophlebitis appeared, and to recognize also many minor forms of thrombosis that recur, at any time developed the picture of phlegmasia alba dolens.

He found pain and soreness on stretching of the calf muscles, a small area of tenderness or, less often, tenderness and induration about the heel and deep in the sole. Following the discovery of such signs, phlegmasia alba dolens might develop in several days to several weeks.

Today's observations have added something. In patients who are to be particularly observed, the calves and ankles are carefully measured — the smallest circumference at the ankle and the largest in the swell of the calf are sufficient — before they undergo the experience, operative or other, that it is thought may lead to a lower-leg thrombosis, special attention should be given to patients over fifty years of age. Each day these observations are

An ulcer operation tested in the experimental laboratory against the powerful capacity of histamine to provoke ulcer in dogs has proved successful for combating the ulcer diathesis in man. The important components of such an operation are extensive gastric resection (75 per cent), employment of a short afferent duodenojejunal loop, a retrocolic anastomosis being made at the suspensory duodenojejunal ligament, and excision of the antral mucosa. Failure on the part of the surgeon to observe all these elements of a satisfactory resection may invite a stomal ulcer. Consistent meeting of these criteria by the surgeon in every gastric resection performed for ulcer will dispel the myth of the intractable ulcer.

Although the prospect of an operation that will preclude recurrent ulcer may be heartening to both patient and surgeon, it is to be hoped that further study will uncover methods of achieving the same end by lesser means. Dispensable as the stomach appears to be, the outlook to ulcer sufferers would be brighter if simpler means were devised to overcome the ulcer diathesis, permitting the patient to keep his stomach intact. Surgeons must continue to be realists, however, wishing-wells are not a solution to the problem. Until a more adequate operation than gastric resection is available, the problem of ulcer must be faced in the light of present knowledge.

REFERENCES

- 1 Beaumont, W. *Experiments and Observations on the Gastric Juice and the Physiology of Digestion*. 280 pp. New York: Peter Smith, 1941.
- 2 Wolf, S., and Wolff, H. G. *Human Gastric Function: A study of a man and his stomach*. 195 pp. New York: Oxford University Press, 1943.
- 3 Kolouch, F., Jr. Direct visual technique for studying chronic ulcer: other injury to exposed mucosal surfaces. *Surgery* 17:541-544, 1924.
- 4 Mann, F. C. Study of gastric ulcers following removal of stomach. *J. Exper. Med.* 23:203-209, 1916.
- 5 Ivy, A. C. Contributions to physiology of stomach. *Arch. Int. Med.* 25:6-31, 1920.
- 6 Mann, F. C., and Williamson, C. S. Experimental production of peptic ulcer. *Ann. Surg.* 77:409-422, 1923.
- 7 Code, C. F., and Varco, R. L. Chronic histamine action. *Proc. Soc. Exper. Biol. & Med.* 44:475-477, 1940.
- 8 Hay, L. J., Varco, R. L., Code, C. F., and Wangenstein, O. H. Experimental production of gastric and duodenal ulcers in laboratory animals by intramuscular injection of histamine in beerwurst. *Am. J. Surg.* 75:170-182, 1942.
- 9 Walpole, S. H., Varco, R. L., Code, C. F., and Wangenstein, O. H. Production of gastric and duodenal ulcers in cat by intramural implantation of histamine. *Proc. Soc. Exper. Biol. & Med.* 61:619-621, 1940.
- 10 Wangenstein, O. H. Ulcer problem. I. Etiology with special reference to interrelationship between vascular and acid peptic factors. II. Characterization of satisfactory operation that will protect against recurrent ulcer. *Canad. M. A. J.* 53:393-395, 1945.
- 11 Graham, R. R. Treatment of perforated duodenal ulcers. *Surg. Gynec. & Obst.* 64:235-238, 1937.
- 12 Allen, A. W., and Benedict, E. B. Acute massive haemorrhage from duodenal ulcer. *Ann. Surg.* 98:736-749, 1933.
- 13 Wangenstein, O. H. Problem of surgical arrest of massive hemorrhage in duodenal ulcer: technique of closing duodenum. *Surgery* 8:275-288, 1940.
- 14 Fast, J. Unpublished data.
- 15 Heuer, G. J., Holman, C., and Cooper, W. A. *The Treatment of Peptic Ulcer Based upon Ten Years' Experience at the New York Hospital*. 118 pp. Philadelphia: J. B. Lippincott Company, 1944.
- 16 Krarup, N. B. On results of medical treatment of peptic ulcer. *Scand. J. Med.* 123:181-207, 1945.
- 17 Hartzell, J. B. Effect of section of vagus nerves on gastric acidity. *Am. J. Physiol.* 91:161-171, 1929.
- 18 Vanzant, F. R. Late effects of section of vagus nerves on gastric acidity. *Am. J. Physiol.* 99:375-378, 1932.
- 19 Dragstedt, L. R. Vagotomy for gastroduodenal ulcer. *Ann. Surg.* 122:973-989, 1945.
- 20 Lahey, F. H. Simple, useful anterior gastroenterostomy. *Surg. Gynec. & Obst.* 78:169-172, 1944.
- 21 *Idem*. Use of identifying "T" tube in common bile duct in gastric resection for duodenal ulcer adherent to bile ducts. *Surg. Gynec. & Obst.* 80:197, 1945.
- 22 Wangenstein, O. H. Method of closing pyloro-antral pouch in antral exclusion operation. *Surgery* 12:731-741, 1942.
- 23 Gavisser, D. Unpublished data.

VENOUS THROMBOSIS AND PULMONARY EMBOLISM*

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PULMONARY embolism, once regarded as an unavoidable accident of surgery, today preoccupies the minds of many clinicians, physicians and surgeons alike. For it is recognized as a threatened complication in the great field of serious diseases, injuries and operations that depress the patient and enforce life in bed.

In the last decade, pathologists have shown that when post-mortem examinations of the legs are thoroughly made, thrombosis is found in the deep veins of the calf in nearly 50 per cent of all cases at autopsy. Much of this thrombosis is terminal and in no sense a cause of death. Yet it fits in with clinical experience in calling attention to a process, relatively frequent in the hospitalized patient, that may readily become a source of embolism.

In the study of thromboembolic disease, it will be convenient to consider first embolism and,

secondly, the diagnosis and treatment of venous thrombosis in the lower limbs.

PULMONARY EMBOLISM

On the clinical side, pulmonary embolism is being recognized by symptoms and signs often regarded in the past as indications of primary disease of the heart and lungs or perhaps as commonplace complaints having no special significance. Hardly any one sign is, in itself, authoritative. It is the combined evidence from several sources that makes the diagnosis, and although in different clinics—those prevalently medical or surgical, for example—emphasis is apt to be placed on one or another group of symptoms, the relative significance of the clinical changes pointing to embolism is indicated in the order of the following paragraphs.

Thoracic symptoms and signs may be expected in about 50 per cent or more of all cases. Pain, although not universal, is the most frequent symptom, it usually takes a pleuritic form, being referred to

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 21, 1946.

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just as successfully by the Swedish school, in reduced doses, three or four times a day. And recently Loewe¹² has shown that reasonably good results can be secured by introducing it intramuscularly in Pitkin's menstruum. Dicumarol, the newer coagulant, acts on the liver to prevent prothrombin formation. Being inexpensive and effectively absorbed when taken by mouth, it is tending to displace heparin. Its successful use at the Mayo Clinic is reported by Barker, Cromer, Hurn and Hughes¹³. Its dosage, however, is almost more difficult to gauge. The same dose in one patient may lower the prothrombin percentage (prolong prothrombin time) dangerously, provoking hemorrhage from the intestinal or genitourinary tract or causing excessive arterial oozing following surgical operation, and yet in another patient it causes no appreciable change in the prothrombin level. Its administration requires experience, skill and daily laboratory analysis of the blood.

Of the two drugs, dicumarol more urgently demands hospital care. Since its withdrawal leads to immediate restoration of prothrombin, vigorous administration of hykinone (artificial vitamin K) is called for if serious hemorrhage is present or threatened.

With such considerations in mind, the anticoagulants may profitably be used as follows: postoperatively for patients over fifty years of age, when no second-stage procedure is contemplated, especially for those subjected to serious abdominal and pelvic operations, but heparin should not be given within seventy-two hours of the operation nor dicumarol within perhaps forty-eight hours. Doubtless, the postoperative uncontrolled period should vary in length with the nature of the operative field, for coronary thrombosis, not only for their effect in preventing the thrombosis in the legs incidental to enfeeblement and confinement to bed but also for their favorable influence on thrombosis in the heart's wall and within its chambers. Wright¹⁴ reports favorably on such treatment.

Vein interruption. Bilateral femoral-vein ligation or section can be recommended for prophylactic purposes in patients over fifty years of age as a preparation for operation in cases of cancer, prostatism and other serious diseases, particularly when a several-stage operation is contemplated, and in the treatment of fractures of the lower limbs requiring immobilization and prolonged treatment, particularly in the affected leg. The femoral vein should be sectioned distal to the profunda branch, for Allen and his associates^{4, 5} find that, at this level, protection against embolism is obtained without noticeable disturbance of the venous return.

Definitive Treatment

One can obtain encouraging evidence in favor of either operative or anticoagulant therapy according to different groups of clinicians. At present, the

trend of medical opinion seems to favor the anticoagulants, but surgical interruption of the venous tree, at one level or another, has a fascinating definiteness that is brought out in the reports from certain hospital centers. I shall attempt to present the problem from several points of view.

Anticoagulants. Bauer¹⁻³ and others of the Swedish school, basing their opinion mainly on postoperative and traumatic cases, hold that heparin, given only on the establishment of an early diagnosis of lower-leg thrombosis by methods that include phlebography, is remarkably effective in controlling not only the local process but also any embolism that may already have occurred. Heparin is given intravenously, in separate doses of 150 mg or less, at regular intervals, without laboratory examinations of the blood. All who have studied their work have been greatly impressed. The Swedish Government furnishes the heparin at a minimal charge — a most important consideration. Recently, dicumarol has been taken up. In the United States this drug is displacing heparin, partly because of its relative cheapness but also because of its greater ease of administration. Whether the intramuscular or subcutaneous use of a menstruum from which heparin can slowly be absorbed will make the older drug as generally acceptable as dicumarol remains to be seen.

Those who believe in treating established venous thrombosis by anticoagulant therapy use it whether or not pulmonary embolism has already occurred, holding that it controls further detachment of thrombus and also prevents thrombosis secondary to the presence of emboli in the pulmonary vessels, favoring healing of the infarct in the lung. Evidently, anticoagulants do not always dispose successfully of the soft, insecure, propagating thrombi in the veins of the lower limb, since fatal embolism has been known to occur on their withdrawal and even during their administration. They appear, however, to render harmless and to heal the thromboses that have not as yet caused embolism, particularly when the process seems to be confined to the lower leg. Thus, they should and probably do, prevent the extension of many thrombi into the popliteal and femoral veins, preserving the useful valves of those vessels.

Anticoagulants, then, may properly be preferred in the treatment of established thrombosis, when laboratory facilities are available and when the conditions calling for treatment are neither continuing nor recurrent, in thrombosis occurring in active life, in early postoperative and post-partum processes apparently confined to the lower leg and in thrombosis associated with any severe brief illness including coronary infarction.

When embolism has already occurred at any stage of thrombosis, the anticoagulants may still be used, although surgical interruption is probably to be preferred, as pointed out below.

repeated. Instead of feeling soft and relaxed, one calf may seem slightly more firm to the grip of the fingers and may prove to be somewhat larger than the other. The muscles may be somewhat irritable, a state brought out by putting the posterior group on the stretch. Deep tenderness may be present along the course of one of the major vessels or perhaps in the popliteal space. But it should be remembered that among the great muscles of the lower leg there are plexuses of veins in great ladder-like systems, in which thrombosis can be tucked quietly away, giving no signs until it becomes so extensive as to occasion discomfort or provoke resistance when the muscles are squeezed or stretched, or until it reaches the popliteal vein, where it may sufficiently obstruct the blood flow to cause edema and cyanosis of the ankle and foot. Yet even these latter signs need not be seen in the patient entirely confined to bed.

A useful proof of deep thrombosis, insufficiently appreciated, is the presence of a thrombosed area in a superficial vein, particularly on the back of the calf. The hardened stretch of vein is all the more noticeable, as a rule, because no varicosity is present as an excuse for a local thrombus. Such a thrombosed vessel is often part of the lesser saphenous system, which communicates freely with the fibular (peroneal) vessels.

It cannot be too strongly emphasized that the more silent and insidious the deep thrombosis, the more dangerous it is, and the more outspoken, the less liable to cause embolism. In a bilateral disease, for example, when one leg is tensely swollen and the other seemingly normal, embolism is threatened less by the swollen limb than by the apparently innocent one. But although any one thrombosis may have more of an inflammatory character, as marked by pain and soreness, than another, all tend to advance in the end toward a femoriliac obstruction. Death, in the early stage, will occasionally occur, or the thrombosis may progress so slowly that it permits a current, of a sort, to pass it for a long time. Basically, there is no true distinction between a quiet thrombosis or phlebotrombosis and the familiar thrombophlebitis, although treatment of the two is somewhat different, and since I am dealing with the thromboembolic problem, I shall devote myself to the quiet, early stage of the disease.

TREATMENT OF THROMBOEMBOLIC DISEASE

It would be ideal if, in every case of early, deep venous thrombosis, the likelihood of embolism could be known—if, for example, one could say that among 100 cases of thrombosis in the lower leg, 10 to 20 were likely to develop embolism and again, that among the 10 to 20 cases of embolism 3 to 5 would be fatal. Such figures are, perhaps, not far from the facts, but from different clinics come various percentages. Among the general run of

postoperative patients, one may expect a higher incidence of thrombosis and embolism than is observed in a group that includes cardiac, prostatic and other extremely ill and elderly persons. Moreover, the diagnosis of venous thrombosis is still a little standardized that consistent figures should not be expected. Again, the age grouping is most important, since embolism, and especially fatal embolism, begins to be seriously threatened only in late middle and advanced age. One had better recognize that in patients committed to bed by operation, accident and serious illness, thrombosis may be encountered so often that it must always be kept in mind, and one should expect embolism, in a mild or serious form, to occur fairly frequently in the early stage of thrombosis. Prophylactic and definitive treatment are based on these considerations.

Prophylactic Treatment

At various times, an astonishing variety of proposals for preventing venous thrombosis in surgical cases has been made, from deep breathing to the giving of dried thyroid gland. Obviously, the first consideration is that the normal activities of the patient should be interrupted as little as possible or, if interrupted, should rapidly be resumed. The term "early ambulation" includes everything intended to restore physiologic normalcy. It cannot be fully protective, since quiet thrombosis may occur without known cause in everyday life, even in young people. Moreover, the very nature of the disease, operation or injury may enforce considerable immobility. Nevertheless, heart disease, most fractures and all surgical operations are now treated with far less confinement to bed than formerly. Above all, the sitting or reclining position in bed, while the legs are relaxed, is to be avoided. And as often as possible the legs must actively be exercised, preferably in elevation, with the aid of an attendant, but if such aid is not at hand, by voluntary contraction and relaxation of muscles by wiggling of the toes and by describing a circle with the forefoot.

Elevation of the foot of the bed favors a return of circulation and avoids venous stasis. Combine with exercise in bed, this procedure has a favorable influence on thrombosis already established. It should therefore be useful as a preventive measure.

Anticoagulants The nature of these chemicals is undoubtedly well known. Heparin, an expensive preparation, acts directly on the blood, delaying coagulation. Its effect is noted by the degree to which the clotting time is prolonged, and since it is rapidly eliminated, the drug must frequently be introduced. Even when administered by continuous intravenous drip, as was done at first both by Murray¹⁰ and by Crafoord,¹¹ it cannot be said to produce an ideal, steadily maintained delay of coagulation for fifteen to twenty minutes (by bedside tests). Actually, it has since been given

t as successfully by the Swedish school, in doses, three or four times a day. And Loewe¹² has shown that reasonably good results can be secured by introducing it intramuscularly in Pitkin's menstruum. Dicumarol, the newer anticoagulant, acts on the liver to prevent prothrombin formation. Being inexpensive and effectively absorbed when taken by mouth, it is tending to replace heparin. Its successful use at the Mayo Clinic is reported by Barker, Cromer, Hurn and Hargraves¹³. Its dosage, however, is almost more difficult to gauge. The same dose in one patient lowers the prothrombin percentage (prolongs the prothrombin time) dangerously, provoking hemorrhage from the intestinal or genitourinary tract or causing excessive arterial oozing following surgical operation, and yet in another patient causes no appreciable change in the prothrombin level. Its administration requires experience, skill and daily laboratory analysis of the blood.

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When embolism has already occurred at any stage of thrombosis, the anticoagulants may still be used, although surgical interruption is probably to be preferred, as pointed out below.

Surgical interruption of veins This method, decidedly favored in this part of the country, has a most attractive quality in that, if ideally performed, it ends all danger of embolism. Its success depends greatly on early diagnosis and exact localization of the thrombus. A distinct advantage is the ease with which the upper femoral vein can be reached under procaine infiltration, so that a general anesthetic is avoided. A disadvantage is the resulting rather sudden venous obstruction at what may be called the common femoral bottleneck, especially when many deep veins in the lower leg and thigh are already more or less occluded by thrombosis. Then, the collateral pathways, adequate in early, local thrombosis, are decidedly insufficient. Yet if the femoral vein is ligated below (distal to) the great branch entering from among the muscles of the thigh (*profunda*), thrombosis may, although rarely, to be sure, short-circuit the obstruction with a fatal result. Anticoagulants may be combined with a superficial femoral section to prevent such an accident, although a period of several days must obviously elapse after the operation before the drugs can be administered. Another disadvantage, which is true of every femoral-vein section for established thrombosis, is that the operation throws out of function the important valvular system of the femoral vein, whether or not the process has already occupied that vein. Thus, even if a thrombus in the calf heals without extension, a considerable readjustment of the venous circulation is required. Actually, in some cases, the local thrombus seems to spread following femoral-vein section, increasing muscular irritability in the lower leg and enforcing a minutely governed and rather prolonged convalescence—a matter too seldom realized by either patients or surgeons.

In spite of such objections as the above, bilateral interruption of the femoral vein should be performed in all cases when anticoagulants cannot be given with proper controls and is a preferred alternative to the use of anticoagulants when thrombosis has advanced into the thigh (as shown by local signs and a considerable duration of the disease), especially when embolism has already occurred. This second indication applies to a great group of cardiac patients, bad fractures in the elderly and postoperative cases in general.

As for the level at which the femoral vein is sectioned, the common femoral vessel, proximal to the *profunda*, for reasons already explained, must be preferred. Into this large vessel a smooth glass tube can be introduced to suck out detachable thrombus. In this way, even the common iliac vein can often be cleared.

Those who believe in performing this operation, even when an obstructive thrombophlebitis is present, hold that the extraction of thrombus from the obstructed and inflamed vein not only lessens such danger of embolism as may exist but also acts

favorably, much as does sympathetic lumbar block by procaine, on the secondary vasoconstriction it causes so much discomfort and edema. This procedure is perhaps well taken, — although the advocates of lumbar sympathetic block maintain that the considerable surgical procedure was unnecessary, — but in any event femoral exploration and section prevent recanalization of the disabled femoral vein and encourage from the beginning a collateral circulation.

Higher interruptions — of the common iliac vein or vena cava — are sometimes desirable. Ligation of the common iliac vein should be used for recurrent persistent processes believed to be confined to the leg. I¹⁵ have elsewhere given reasons for holding that it offers a collateral circulation decidedly better than is permitted by a common femoral interruption. The approach to both common iliac vessels extraperitoneal, requiring a general anesthetic, is sometimes difficult, especially on the left.

Ligation of the vena cava is a last resort in the presence of otherwise uncontrollable embolism, especially when the causal thrombosis is bilateral and unlocalizable. Although statements to the contrary are often made, the operation is one requiring experience and skill in approaching and handling large blood vessels. At times, it must be accepted as superior in effectiveness to any other procedure, operative or medicinal.

* * *

This discussion has perhaps left a sense of confusion. Should the anticoagulants or operative procedure be preferred as the ideal treatment for threatened actual venous thrombosis and for threatened actual embolism? I recognize that the present trend is toward a greater use of the anticoagulants. If far this tendency will go, I am unable to say. At the moment, I have offered a reasonable scheme for making use of one method or the other, observing that in some circumstances there is a choice between them. On behalf of surgery, I beg that it be employed only when it is fully understood what particular operative procedure may be expected to accomplish. I urge that the anticoagulants be used only when accurate, routine blood studies are available. Undoubtedly, as experience widens, definite indications for the use of operative or clinical methods of preventing and treating thrombosis in the veins of the lower limbs will be available.

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REFERENCES

1. Bauer, G. Roentgenological and clinical study of sequelae of thrombosis. *Acta chir. Scandinav.* 86 (Supp. 74) 116, 1942.
2. *Idem*. Thrombosis following leg injuries. *Acta chir. Scandinav.* 229-248, 1944.
3. *Idem*. Heparin therapy in acute deep venous thrombosis. *J. A. M. A.* 131:196-203, 1946.
4. Allen, A. W., Linton, R. R., and Donaldson, G. A. Thromboembolism: review of 202 patients treated by femoral vein interruption. *Ann. Surg.* 118:728-740, 1943.
5. *Idem*. Venous thrombosis and pulmonary embolism. *J. A. M. A.* 128:397-503, 1945.

- Hampton, A O and Castleman B. Correlation of postmortem chest teleortogenograms with autopsy findings with special reference to pulmonary embolism and infarction. *Am J Roentgenol* 43 305-326 1940
- Fleischner, F G, Hampton A O and Castleman, B. Linear shadows in lung (interlobar pleuritis atelectasis and healed infarction). *Am J Roentgenol* 46 610-618 1941
- Schneider, A. Intravenous clotting. *Surgery* 17 240-263 1945
- Conner, L. A. Thrombophlebitis and its pulmonary complications. *New Eng J Med* 222 125-130 1940
- Murray G. Heparin in thrombosis and blood vessel surgery. *Surg., Gynec & Obst* 72,340-344 1941
- Crafoord C. Heparin as prophylactic against postoperative thrombosis. *Acta med Scandinar* 107 116-122 1941
- Loewe L., Rosenblatt P., and Hirsch E. Venous thromboembolic disease. *J A M A* 130 386-393, 1946
- Barker N W, Cromer H E, Hurn M and Waugh J M. Use of dicumarol in prevention of postoperative thrombosis and embolism with special reference to dosage and safe administration. *Surgery* 17 207-217 1945
- Wright I S. Experiences with dicumarol (3, 3 methylene-bis-[4-hydroxycoumarin]) in treatment of coronary thrombosis with myocardial infarction preliminary report. *Am Heart J* 32 20-31 1946
- Homans J. Deep quiet venous thrombosis in lower limb preferred levels for interruption of veins iliac sector or ligation. *Surg., Gynec & Obst* 79 70-82 1944

THE SIGNIFICANCE OF EOSINOPHILIA IN ABDOMINAL COMPLAINTS OF AMERICAN SOLDIERS

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IN THE Southwest Pacific the characteristics of many tropical diseases acquired by American soldiers differed from those described in textbooks. Medical officers suspected new syndromes, but laboratory personnel were frequently unable to confirm these impressions with routine methods. The lack of specific diagnostic evidence often forced diagnosis of psychoneurosis. In the course of time, it was possible to evaluate certain criteria and to devise practical technics that were helpful in differentiating the neurotic patients from those with usual manifestations of the usual tropical diseases. Some of these methods have been described in previous publications. For example, the proper interpretation of chromatin dots and pigmented leukocytes in thick smears stained in an unconventional manner helped confirm the diagnosis of malaria in a substantial number of patients with vague, non-specific febrile reactions.¹ Attention to the significance of high degrees of eosinophilia aided in establishing a diagnosis of filariasis when clinical criteria were lacking.² In a large group of patients with gastrointestinal disorders, controlled studies utilizing practical technics helped differentiate functional from organic disorders.^{3, 4} A study of hematology values clarified the significance of eosinophilia in American soldiers.⁵

After thirty-six months of clinical and laboratory experience in the tropics, the evidence was convincing that high degrees of eosinophilia in American soldiers usually indicated helminthic infections. On the basis of this premise, every case of unexplained eosinophilia was studied intensively. Recently, the records of these patients were reviewed. As a rule they were combat infantrymen hospitalized for vague but incapacitating intestinal complaints. Hookworm ova were found in the majority of cases,

and Strongyloides in some. In the latter, examination of duodenal fluid was the only method of diagnosis. The similarity of symptoms between the patients with helminthic infections and others previously studied with anxiety neuroses was striking.

MATERIAL AND METHODS

A large Army station hospital with thirty-six months' service in the South and Southwest Pacific theaters of operation had a substantial number of patients with high degrees of eosinophilia whose causes were not being determined by routine methods. During 1944-1945 in New Guinea, the medical and laboratory services established an "unexplained eosinophilia ward" to study patients in whom laboratory studies on the respective wards did not clarify the cause for eosinophilia.

Clinical studies. Histories in the form of questionnaires, with special reference to allergic diatheses, systemic complaints and exposure to parasitic infections, were utilized. Physical examinations were detailed and frequent. Special diets were available, and recreational facilities in the hospital were excellent for New Guinea.

Laboratory studies. Detailed analyses of the blood and urine were made. Diagnostic gastric and duodenal intubations, roentgenograms of the gastrointestinal tract, using contrasting mediums, and of other systems when indicated, and proctoscopies were performed routinely on the last 25 patients. Each fecal specimen passed during the first three days was studied for ova and parasites by a concentrated method.⁶ Thereafter, at weekly intervals, a dose of magnesium sulfate was administered, and all stools passed on that day were examined. The blood, urine, gastric and duodenal fluid and prostatic secretions were also examined for ova and parasites. An eosinophilia of 9 per cent or more was considered significant. Cutaneous testing materials for specific allergens were not available.

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RESULTS

Fifty-nine patients with unexplained eosinophilia were studied. Forty-seven (79 per cent) were found to have intestinal helminthic infections. Of this group, 42 (89 per cent) had hookworm disease, whereas 5 (11 per cent) had strongyloidiasis. In the

TABLE 1 Pertinent Data in 59 Patients with Eosinophilia

DATUM	EOSINOPHILIA OF		
	HOOKEWORM DISEASE* (42 CASES)	STRONGYLOIDIASIS† (5 CASES)	UNDETERMINED ORIGIN‡ (12 CASES)
	NO. OF CASES	NO. OF CASES	NO. OF CASES
Admission diagnosis			
Psychoneurosis (abdominal complaints)	11	3	5
Appendicitis	4	-	1
Gastroenteritis	4	1	1
Hookworm disease	5	-	-
Peptic ulcer	3	-	1
Gastritis acute	2	-	-
Duodenitis acute	1	-	-
Colitis, acute	1	-	-
Dysentery acute	-	1	-
Sciatica	1	-	-
Arthritis	1	-	1
Surgical conditions	5	-	-
Malaria	1	-	-
Scrub typhus	2	-	-
Bronchitis	1	-	1
Cephalgia	1	-	-
Hepatitis	1	-	2
Dermatosis	-	-	-
Signs and symptoms			
Abdominal distress	29	5	7
Anorexia	14	5	8
Nausea	14	1	5
Weakness	13	3	5
Fatigue	13	3	5
Weight loss	12	3	5
Vomiting	10	3	3
Nervousness	10	4	5
Headache	8	1	5
Joint pains	6	-	3
Palpitation	5	-	4
Tremors	3	-	-
Nightmares	3	2	6
Occurrence of symptoms			
During or after combat	26	4	5
Before combat	4	1	1
On Louisiana maneuvers	1	-	1
Prior to induction	9	-	5
Previous hospital admission for psychoneurosis	10	4	5

*The average onset of symptoms after exposure was one hundred and forty seven days, the average duration of symptoms before hospitalization was one hundred and thirty days and the diagnosis was made, on the average, eighteen days after admission.

†The average onset of symptoms after exposure was twenty four days, the average duration of symptoms before hospitalization was one hundred days and the diagnosis was made, on the average, forty-one days after admission.

‡The average duration of symptoms before hospitalization was two years.

12 other cases the cause for the eosinophilia could not be determined.

The findings in the three groups of patients described are presented in Tables 1 and 2.

Hookworm Disease

Of 42 patients with hookworm disease, 29 (69 per cent) were admitted with diagnoses referable to the gastrointestinal tract, including psychoneurosis, gastroenteritis, appendicitis, peptic ulcer, duodenitis, colitis and hookworm disease. In 2 cases the diagnosis on admission was acute rheumatoid arthritis, and 11 patients were hospitalized for con-

ditions not related to the helminthic infection. The patients were studied because eosinophilia was found on routine blood examination. Ten patients (25 per cent) of the entire group had previously been hospitalized with the same complaints.

The predominant symptom was abdominal distress, which most patients described as an intermittent, severe, cramplike pain in the epigastrium that usually occurred after eating and lasted a few hours. The pain was more intense at night and was not relieved by food, alkalies or defecation. Others complained of dull, aching sensations in the periumbilical region, and a few had inconstant pains in the midabdominal area that radiated to the chest or back. Some patients were disturbed by constipation alternating with soft, mushy movements, although in the majority of cases the bowel habits were normal. Almost all patients emphasized anorexia, nausea, weakness, fatigue, weight loss, vomiting and nervousness. Less frequent complaints were headache, palpitations, tremors and night mares. Physical examinations were not helpful.

The majority of patients had been sufficiently exposed during combat patrols to acquire hookworm disease. Usually, they had slept on the ground, swum in streams near native villages or eaten unpackaged bread dropped from parachutes. On the average, the onset of symptoms after probable exposure was one hundred and forty-three days, and one hundred and thirty additional days elapsed before symptoms became severe enough to warrant hospitalization. Ordinarily a patient was hospitalized twenty-one days before he was transferred to the ward for study, and the diagnosis was most frequently made during that period.

The average red-cell count was 4,300,000, with a hemoglobin of 87 per cent (Sahli). As a rule, there was a slight leukocytosis, although the eosinophil count was high (9 to 36 per cent). Such high counts were usually found on admission and persisted after discharge. Ova of *Necator americanus* were often found in the feces during the third week of study. Other laboratory findings were irrelevant.

Thirty-three patients received tetrachlorethylene in the prescribed manner.⁷ The results of treatment were considered successful in 28 cases, although symptoms in a milder form usually persisted and ova were occasionally found. In the other cases neither the symptoms nor the parasites seemed affected, in spite of several courses of anthelmintic therapy. Nine patients treated with carbon tetrachloride responded in a like manner.

The following cases were typical of the group with hookworm disease.

CASE 1. A 30-year-old combat infantryman was admitted to the hospital because of headache, dizziness and nausea of 1 week's duration. On the day before admission he had struck his head accidentally. The admission tag stated, "Discharge quickly—patient is neurotic, with fixations of pain in head and stomach."

30 months before admission, the patient first complained of "headaches" followed by sharp, knifelike pain in the epigastrium occurring daily in the late afternoon and persisting until morning. Nausea was frequent, but vomiting rare. Neither food nor alkalies relieved the pain. During the following month he became irritable, discontented and nervous. He attended sick call frequently, but medication did not help. The accident precipitated admission to the hospital.

Physical examination was essentially negative. Laboratory studies revealed an eosinophil count of 14 per cent. Three stool examinations (concentrated method) were negative.

The patient was transferred for further study to the "eosinophilia ward," where the past history was found to be contributory. He had been in the combat zone in New Guinea for 1 year prior to the onset of symptoms, but denied breach of sanitary precautions. Laboratory studies over a period of 3 weeks were negative, these included several stool examinations and two duodenal intubations. The patient

was ministered. The patient recovered but during the week developed a mild diarrhea. Concomitantly a leukocytosis and an eosinophil count of 11 per cent were found. A stool examination was negative, and the diarrhea receded without specific therapy.

Two weeks later the patient complained of nausea, anorexia and abdominal distress. He was transferred to the hospital with a diagnosis of psychoneurosis. On arrival he was irrational and had hyperactive reflexes. A diagnosis of hysteria was made.

Six weeks later the patient was transferred to the "eosinophilia ward." Questioning revealed that in 1942 he had been hospitalized for a fractured skull. Within the following 6 months he had had two convulsions and several violent temper tantrums. He had been inducted into the Army in January, 1943. In August, while on maneuvers, he had had urticaria and hay fever. En route to New Guinea in May, 1944, he had been operated on for appendicitis. During combat patrols in October 1944, he had swum in fresh-water streams and eaten native food. He had been sent to rest

TABLE 2 Laboratory Data in 59 Patients with Eosinophilia

DATUM	HOOKWORM DISEASE	STRONGYLOIDIASIS	EOSINOPHILIA OF UNDETERMINED ORIGIN
Blood			
Red-cell count	4,500,000	4,000,000	4,400,000
Hemoglobin (Sahli)	87%	87%	86%
Eosinophil count	9-36%	9-60%	9-33%
Sedimentation rate	Normal	Increased (1 case)	Increased (2 cases)
Sugar	Normal	Normal	Normal
Nonprotein nitrogen	Normal	Normal	Normal
Urea nitrogen	Normal	Normal	Normal
Creatinine	Normal	Normal	Normal
Uric acid	Normal	Normal	Increased (1 case)
Total protein	Normal	Low (1 case)	Normal
Albumin globulin ratio	Normal	Reversed (1 case)	Normal
Icterus index	Normal	High (1 case)	Normal
Gastric contents			
Acidity	Normal	Normal	Normal
Microscopical examination	Normal	Larvae (1 case)	Normal
Duodenal contents			
Appearance	Normal	Mucoid (all cases)	Mucoid (3 cases)
Microscopical examination			
Epithelial cells and leukocytes	Absent	Increased (all cases)	Increased (3 cases)
Larvae	Absent	Present	Absent
Feces (concentrated specimen)			
Ova	Present	Present (1 case)	Absent
Larvae	Absent	Present (1 case)	Absent
Adult worms	Absent	Absent	Absent
Proctoscopic examination	Normal	Ulcerative colitis (1 case)	Normal
Gastrointestinal x ray film	Normal	Normal	Pylorospasm (1 case)

was treated with iron and vitamins and returned to duty, because the symptoms had improved.

Three days later, he was readmitted with severe epigastric distress. Physical examination revealed some spasm and tenderness over the right rectus muscle, but this receded promptly after an enema. Eosinophilia was still present. A second gastrointestinal series and two stool specimens examined a week apart were normal. During the 3rd week, ova of *N. americanus* were found in the feces. Treatment was instituted. The symptoms subsided and the patient returned to duty within 3 weeks.

In this case a diagnosis of hookworm disease was made seven weeks after a careful study had been initiated, and four months after the onset of abdominal complaints. This case illustrates that a long period of observation may be necessary before a diagnosis of hookworm disease can be established.

CASE 2 A 22-year-old infantryman was admitted from combat to a field hospital with bronchopneumonia. X-ray examination confirmed the diagnosis, and penicillin was ad-

ministered on several occasions but had returned to actual combat of his own volition.

The patient was admitted to the study ward during February, 1945. Physical examination revealed a sullen, uncooperative soldier, who showed evidence of marked weight loss. Laboratory studies revealed a white-cell count of 25,500, with 24 per cent eosinophils. Five stool examinations were negative. A positive diagnosis of hookworm disease was made during the following week. Satisfactory recovery was made after two courses of an anthelmintic.

This case illustrates the difficulties of differentiation. The entire syndrome could have been helminthic in origin, but in view of the previous neuropsychiatric disturbance, it seemed more plausible that the helminthic infection merely precipitated a severe emotional upset.

Strongyloidiasis

The 5 patients with strongyloidiasis were admitted with the following diagnosis "Psycho-

RESULTS

Fifty-nine patients with unexplained eosinophilia were studied. Forty-seven (79 per cent) were found to have intestinal helminthic infections. Of this group, 42 (89 per cent) had hookworm disease, whereas 5 (11 per cent) had strongyloidiasis. In the

TABLE 1 Pertinent Data in 59 Patients with Eosinophilia

DATUM	EOSINOPHILIA OF		
	HOOKEWORM DISEASE* (42 CASES)	STRONGYLOIDIASIS† (5 CASES)	UNDETERMINED ORIGIN‡ (12 CASES)
	NO. OF CASES	NO. OF CASES	NO. OF CASES
Admission diagnosis			
Psychoneurosis (abdominal complaints)	11	3	5
Appendicitis	4	—	1
Gastroenteritis	4	—	1
Hookworm disease	3	—	—
Peptic ulcer	3	—	1
Gastritis, acute	2	—	—
Duodenitis, acute	1	—	—
Colitis, acute	1	—	—
Dysentery, acute	—	1	—
Sciatica	1	—	—
Arthritis	1	—	1
Surgical conditions	5	—	—
Malaria	1	—	—
Scrub typhus	2	—	—
Bronchitis	1	—	1
Cephalgia	1	—	—
Hepatitis	1	—	—
Dermatosis	—	—	2
Signs and symptoms			
Abdominal distress	29	5	7
Anorexia	14	5	8
Nausea	14	1	5
Weakness	13	3	5
Fatigue	13	3	5
Weight loss	12	3	5
Vomiting	10	3	3
Nervousness	10	4	5
Headache	8	1	5
Joint pains	6	—	3
Palpitation	5	—	—
Tremors	3	—	4
Nightmares	3	2	6
Occurrence of symptoms			
During or after combat	26	4	5
Before combat	4	1	1
On Louisiana maneuvers	1	—	1
Prior to induction	9	—	5
Previous hospital admission for psychoneurosis	10	4	5

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poison ivy. During combat patrol, in August, 1944, he had bloody dysentery. Laboratory studies revealed an eosinophil count of 32 per cent, and two examinations of the duodenal fluid revealed a marked epithelial exudate associated with neutrophilic and eosinophilic polymorphonuclear leukocytes. No ova or parasites were found. The patient was treated with iron and vitamins. The symptoms improved, and the eosinophil count receded to 12 per cent. He returned to duty 3 months later, when he was somewhat recovered.

This case represents a diagnostic problem. The patient had always lived in a region where hookworm is endemic, he had a history of allergy, as well as gastrointestinal symptoms, that predated tropical climate, and was convalescing from infectious hepatitis. Clinically, this patient resembled those in cases of strongyloidiasis, and the duodenal fluid simulated the fluid of patients with that finding. Yet, the absence of larvae, this finding is of questionable significance.

CASE 6 A 20-year-old noncombatant soldier was admitted to the hospital with a diagnosis of "generalized myositis." He complained of a stiff neck and aching legs of 2 months' duration. Physical examination revealed a thin, asthenic man, who held his head stiffly to one side. The right sternocleidomastoid muscle was spastic and tender to palpation. Laboratory studies were essentially negative except for an eosinophil count of 28 per cent.

The patient was transferred to the study ward. He had been born and had lived on a farm in Missouri. Ever since childhood the legs had ached and the joints had occasionally been stiff. Since induction into the Army he had complained of fatigue on several occasions, and during his overseas service had been hospitalized with that complaint three times in 3 months. Roentgenograms of the muscles were negative for calcifications. An elevated blood ureic acid was found on two occasions, but other laboratory studies were negative. The eosinophil count receded to 11 per cent without specific treatment. The patient was returned to the United States unimproved.

Simultaneous tests for specific allergins, especially tests for trichina, might have clarified the diagnosis in this case. Clinically, the patient had rheumatoid arthritis. He could not be classified as having hookworm disease or strongyloidiasis.

DISCUSSION

Hookworm disease acquired in the Southwest Pacific differs materially from the disease as it is known in the southern United States. It seems likely that the symptoms reflect allergic or invasive phenomena rather than anemia, which is often responsible for the classic manifestations. The fact that it was frequently impossible to find ova in the feces during a period when the symptoms were most distressing strengthens this impression. Allen⁸ reported that eosinophilia was present in soldiers long before hookworm ova could be found. Eggs were found, however, when the patients were studied long enough. This was also observed in the majority of the cases discussed herein.

Chacon⁹ described early symptoms of ankylostomiasis in Porto Ricans. Violent headaches and dizziness were most frequent initial complaints. Pain in the knees and waist, fatigue, sleepiness and palpitation appeared early in the disease. Three other symptoms were consistently present: epigastric

gastric pain, — as well as a feeling of fullness after meals, — mild diarrhea and "watering of the mouth." Soldiers in New Guinea had comparable complaints. Recently, Rogers and Dammin¹⁰ reported a syndrome occurring in American soldiers stationed in Assam and Burma characterized by acute gastrointestinal symptoms, severe diarrhea and eosinophilia. No difficulty in finding hookworm ova in the feces was encountered, however, when specimens were prepared by a flotation centrifugation method. In addition, gastrointestinal roentgenograms showed peculiar cogwheel abnormalities of the small intestine. It appears that the cases discussed above and those reported by Allen represented minimal infestations, whereas those reported by Rogers and Dammin indicated either a heavier parasitemia or an extreme response to the allergin.

Eosinophilia is a most important diagnostic lead in obscure parasitic infections. Although it must be interpreted as a nonspecific finding associated with a multiplicity of allergic diseases, an increasing eosinophilic leukocytosis usually indicates helminthic infection. Similarly, when high eosinophil counts (9 per cent or more) are consistently associated with dengue, scrub typhus, infectious hepatitis, malaria, the dermatoses and the allergic respiratory diseases, in which a value of 6 per cent is average, nematode infection should be suspected. Eosinophilia, which is usually present weeks before the parasite can be demonstrated, generally persists long after treatment has been considered adequate. In the absence of specific cutaneous tests for allergins, eosinophilia must be regarded seriously.

The patients with strongyloidiasis presented interesting diagnostic problems. They were shunted from hospital to hospital, being considered psychoneurotic. They remained on the wards for weeks, obviously ill, but without presenting any positive diagnostic criteria other than eosinophilia. Finally, when the duodenal fluid was examined, motile larvae were found without difficulty. Yet stool examinations repeatedly failed to reveal the larvae, even when they were known to be present in the duodenum. Perhaps, in minimal infections, the parasites are not irritating enough to cause diarrhea. It is usually in that type of stool that the larvae are found.

Duodenal intubation as a diagnostic method in strongyloidiasis has not been stressed sufficiently. It is not a difficult procedure,¹¹ but it takes time. Fluoroscopy speeds the operation but is not essential. Normally, the alkaline duodenal fluid is devoid of parasites, evidence of an inflammatory reaction or a significant amount of tissue debris. *N. americanus* and *S. stercorarius*, after they have completed their invasive cycle, settle in the small intestine, where their eggs are laid. In addition to fecundity, the worms are said to liberate toxins that cause disturbing nonspecific and gastrointestinal symptoms. Whereas hookworm ova hatch in the feces outside

neurosis manifested by vague abdominal complaints."

The general pattern of the complaints was similar to that in patients with hookworm disease. There was less specificity, however. Abdominal pain occurred at any time during the day or night, varying in intensity. Often, it was cramplike, it was more frequently described as an "ache that was always there." Other disturbing features were increasing weakness, irritability and nervousness. There was evidence of marked weight loss and asthenia.

Four patients gave adequate histories of possible exposure. The average onset of symptoms was twenty-four days after exposure, but another hundred days elapsed before the distress was severe enough to warrant hospitalization. The patients were hospitalized several months before examination of the duodenal fluid clarified the diagnosis.

The examination of concentrated specimens of duodenal fluid was diagnostic in every case. In 4 patients, motile, rhabditiform larvae of *Strongyloides stercoralis* were found only in the duodenal juice, whereas in 1 larva were also found later in a diarrheal stool. The appearance of the duodenal contents suggested chronic inflammation. There were large amounts of columnar epithelium and mucous shreds, as well as many round cells, neutrophils, eosinophils and erythrocytes. In 4 cases examinations of the feces were consistently negative.

Treatment consisted of 25 cc of a 1 per cent aqueous solution of gentian violet, administered intraduodenally. The symptoms persisted in spite of repeated treatment, although 1 patient improved temporarily. The following cases were characteristic.

CASE 3 A 28-year-old combat infantryman was admitted with the diagnosis of "psychoneurosis manifested by vague intestinal pains" in July, 1944. While on combat patrol, 7 weeks previously, he had been seized with severe aching cramps across the epigastrium. Nausea, vomiting and diarrhea were conspicuously absent. Because of recurrent attacks, the patient was admitted to a field hospital, where examination, including a gastrointestinal x-ray series with contrasting mediums, was negative. After 3 weeks he was evacuated to this hospital for psychiatric evaluation.

Physical examination showed the patient to be ill and emaciated, with a peculiar gray pallor. Routine studies were negative except for a moderate leukocytosis and an eosinophil count of 35 per cent.

The patient was transferred to the study ward, where questioning revealed that he had been in combat in the Solomon Islands in 1943, with no sequelae. While on combat patrol in New Guinea during the following summer, he had swum in a stream adjacent to a native village and had eaten native food and unpackaged bread dropped by parachute. Detailed laboratory studies during October and December, 1944, had been negative, as were many stool examinations. During the 3rd month of study the duodenal fluid was examined. On the first specimen 8 to 12 actively motile larvae within clear refractile shells (*S. stercoralis*) were found. A large number of columnar epithelial cells, mucous shreds, round cells and neutrophils and eosinophilic leukocytes were also observed. Specific treatment was initiated, with some relief in the following week. During the 3rd week the symptoms returned in a milder form. Duodenal intubation was repeated. Larvae were not found in the fluid, but a moderate amount of exudate was present. Treatment was repeated, but abdominal unrest persisted. The patient was returned to the United States for further study.

This case demonstrates that negative stool examinations cannot eliminate the possibility of helminthic infections. This patient was hospitalized much longer than usual, because the medical officer was impressed by his complaints. Duodenal intubation clarified the reason for the eosinophilia, and a diagnosis of psychoneurosis was averted. It is possible that a neurosis was acquired during the long period of hospitalization.

CASE 4 A 23-year-old combat infantryman was transferred from a field hospital with a diagnosis of "psychoneurosis manifested by vague abdominal complaints." During May, 1944, while on combat patrol, he had noticed constant needle-like pain in the right epigastrium that was temporarily relieved by food. At night, the pain was intense, but vomiting followed eating. The patient was hospitalized and treated with antispasmodics, returning to duty in 2 weeks. He was readmitted 2 months later because the symptoms were worse. During the interim he had lost 40 pounds of weight and had become extremely nervous. He was transferred to this hospital in September, 1944. Routine examinations were negative except for a moderate leukocytosis and an eosinophil count of 50 per cent.

The patient was transferred to the "eosinophilia ward." During combat in 1942, he had been hospitalized twice for projectile vomiting. Later, in Australia, a diagnosis of psychoneurosis was made. When he returned to combat in May, 1944, he admitted breaches in sanitary precautions.

Three months after readmission examination of the duodenal contents revealed a few actively motile rhabditiform larvae of *S. stercoralis* in each specimen. There was a large amount of epithelial debris and cellular exudate. Eosinophils were abundant. The symptoms persisted in spite of adequate therapy, although larvae were not found again. Evacuation to the United States seemed indicated.

This case also demonstrates the difficulty in differentiating neurotic complaints from symptoms caused by helminths. The past history suggested that the patient was neurotic. The high degree of eosinophilia, however, was a diagnostic lead, and proves that this finding is significant. Again, an unstable personality may explain why complete regression of symptoms was not achieved.

Eosinophilia of Undetermined Origin

In 12 cases no cause for the eosinophilia was found. The symptoms in 9 simulated those in the soldiers with helminthic diseases. All patients had a history of possible exposure, and many had previously been hospitalized for the same complaints. Three patients had histories of allergies and non-specific complaints that predated Army service.

Laboratory studies were negative, although the duodenal contents in 3 of 9 cases resembled those in which *S. stercoralis* had been found, except that larvae were absent.

CASE 5 A 22-year-old infantryman was admitted with a diagnosis of "psychoneurosis manifested by vague intestinal symptoms." The main difficulty was eructation of sour material after every meal. This symptom had begun in 1943, shortly before overseas assignment. In September, 1944 in New Guinea, the patient was hospitalized for gastritis and hepatitis. Because of the persistence of eructations and of a throbbing ache in the epigastrium, he was evacuated to this hospital. Physical examination was essentially negative, but laboratory studies revealed an eosinophil count of 36 per cent.

The patient was transferred to the study ward. He was a native of Mississippi. He had always been allergic to tomatoes.

MEDICAL PROGRESS

CANCER

GRANTLEY W TAYLOR, M.D.*

BOSTON

POSTWAR survey of practice and theory in relation to cancer problems shows little fundamental change in comparison with the prewar years, though in some fields there have been modifications and shifts in emphasis. This review can make pretense of being complete, but it seems desirable to comment on certain aspects of the problem.

Carcinoma of the Mouth

There appears to be an increasingly accurate dissemination regarding the respective fields of radiation and surgery in the treatment of primary intracranial carcinoma.^{1,2} The former division into separate camps, with exclusive use of radiation in some clinics and exclusive use of surgery for operable cases in others, has given place to a willingness to concede the value and merit of the other approach. This comes about through accurate critical analysis of the results achieved in cases of carefully defined location, extent and histology. Radical surgery is applicable primarily in small accessible tumors that are of a relatively low grade of malignancy. The more extensive high-grade lesions are better suited to radiation therapy. The results of this treatment have improved with the employment of greater dosage. There has also been clarification of the indications for neck dissection, as well as of the benefit that may be expected as a result of dissection.³

Carcinoma of the Larynx

Similar clarification is desirable in laryngeal carcinoma. Cutler⁴ has presented an impressive series of cases treated by a modified Coutard method of radiation. Schall⁵ and others have successfully employed laryngectomy in a large number of cases. It is probable that many of the patients treated by laryngectomy might have been cured by radiation. It is also possible that certain of the cases that proved to be refractory to radiation might have been successfully treated by laryngectomy. Analysis of the clinical and pathological characteristics that contribute to a successful outcome by one or another method of treatment should be carried out at every opportunity.

Mixed Salivary Tumors

In spite of the sustained interest of McFarland⁶ in the mixed salivary tumors, their origin and pos-

sible relation to the development of carcinoma remain obscure. In general, these tumors are smaller when the patients first seek advice than they were several years ago. Earlier textbooks describe the characteristic tumor as the size of a walnut, or even an egg. In recent experience, such large tumors are distinctly unusual in this community. The apparent tendency to evolve toward benignancy with increased duration and size, noted by McFarland, may be explained by the fact that the larger tumors are operated on with more respect and more radically. The propensity to recur following simple excision has led to increasing employment of the Adson-Ott operation⁷ in which the entire gland superficial to the facial nerve is resected, including the tumor. The excellent anatomical studies of this region by McCormack et al.⁸ should be reviewed by all surgeons who undertake to perform this operation.

Carcinoma of the Thyroid Gland

There is general agreement that thyroid carcinoma usually originates in a pre-existing pathologic condition of the gland, frequently in a solitary nontoxic nodule. In fact, the incidence of carcinoma in solitary nontoxic nodules may be as high as 24 per cent,⁹ or even higher.¹⁰ There is general acceptance of invasiveness and blood-vessel invasion as criteria of malignancy. The problem at once arises concerning how much further surgery may be necessary when the pathologist unexpectedly returns a report of carcinoma in an apparently innocent nodule that has been removed at operation.

The high incidence of carcinoma in these nodules argues that excision be abandoned. Wide resection of the involved area or complete excision of the lobe should be carried out. This procedure is probably sufficiently radical when there is no clinical evidence of malignancy and when there is no pathological evidence of invasion of the gland capsule. When malignancy is suspected or when there is evidence of invasion of the gland capsule at operation, it is essential to carry out block dissection of the affected side. This involves removal of the sternomastoid, sternohyoid, omohyoid and sternothyroid muscles, the internal jugular vein from the junction with the subclavian vein to the lower pole of the parotid gland and the lymphoid tissue and fat from the anterior border of the trapezius muscle to the midline.

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the body, the eggs of *Strongyloides* hatch in the small intestine, causing a catarrhal inflammation characterized by a round-cell and eosinophilic exudate^{12, 13} Usually, a persistent diarrhea results in which free motile rhabditiform larvae may be found.

An eosinophilic exudate has been observed in the duodenal fluid in strongyloidiasis but not in that from patients suffering from hookworm disease. Neither the hookworm adult nor ova could be found in the duodenum even at a period when it was not yet found in the feces. In some cases in which eosinophilia remained unexplained, the duodenal fluid suggested an allergic exudate. The significance of inflammatory reactions, however, as portrayed by the duodenal juices, must be regarded with caution, because comparable exudates have been observed following the ingestion of magnesium sulfate.¹⁴

During this hospital's period of service a substantial number of cases were diagnosed as psychoneurosis. A significant number with the syndrome described in this paper fell into that category. Their symptoms may have been essentially helminthic in origin, but on the other hand, the conditions of jungle warfare may have been responsible for the display of neurotic tendencies. Certainly, long periods of medical treatment without relief or even proper diagnosis contributed to puzzling complaints. The consensus was that these patients were neurotic regardless of their infections. Because treatment was unsatisfactory, as manifested by the persistence of ova or larvae and eosinophilia after adequate anthelmintic therapy, perhaps a definite opinion of the mental reactions should be held in abeyance until additional reports of the early manifestations of helminthic diseases are collected.

Certain criteria that Rush³ established in a group of patients with anxiety neurosis studied in this hospital help differentiate the true psychoneurotic patients from those with pathologic findings to account for their complaints. The symptoms manifested by Rush's group hardly differed from those in patients with helminthic disease, and yet the type of patient differed. The true neurotic patient had been in the tropics only a short time before he was hospitalized, he was never in combat because he was "always weeded out", his chief complaint was abdominal pain, which was frequently relieved after defecation, he overaccentuated any single complaint, and this varied from day to day, he showed no evidence of weight loss or malnutrition, and, finally, intestinal parasites were never found, nor was there an eosinophilia. On the other hand, patients with proved or suspected helminthic diseases, who seemed of a different temperament, were consistent in their complaints. Positive or suggestive laboratory findings were always present.

Prior to this study, the causes were found in approximately 40 per cent of soldiers with eosinophilia admitted to the hospital. With special efforts, the reasons for eosinophilia in the majority of cases were

clarified. It was gratifying that a diagnosis of psychoneurosis was deferred in a substantial number. Although neurotic tendencies were outstanding in many of the patients studied, evidence is being accrued that the early symptoms of helminthic infections were different from those that were expected.

SUMMARY

Fifty-nine American soldiers hospitalized in New Guinea were studied for unexplained eosinophilia. Forty-seven (79 per cent) were found to have intestinal helminthic infections. Forty-two (71 per cent) had hookworm disease, 5 (8 per cent) had strongyloidiasis and 12 (20 per cent) presented no demonstrable cause for the eosinophilia.

The majority of patients were admitted to the hospital because of abdominal complaints. A substantial number were classified as psychoneurotic prior to study. The predominant symptom was intermittent, cramplike epigastric pain. Anorexia, nausea, vomiting, weakness, fatigue, nervousness and weight loss were prominent. Physical examination was negative.

The onset of symptoms usually occurred four and a half months after probable exposure, and the symptoms became severe enough to warrant hospitalization during the next four and a half months.

Laboratory studies revealed a persistently high eosinophil count (9 per cent or more). In patients with hookworm disease, ova were found in the feces, usually during the third week of the study. Examination of duodenal fluid was the only method of diagnosing 4 of 5 cases of *Strongyloides* infection. In these patients, larvae were not found in the feces.

The diagnosis of psychoneurosis may not be warranted in the veteran with the syndrome described in this report.

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REFERENCES

- Denhoff, E., and Piper, B. C. Laboratory aids in diagnosis of malnutrition. *J. Lab. & Clin. Med.* 29: 518-524, 1944.
- Hodge, I. G., Denhoff, E., and VanderVeer, J. B. Early blastitis (bancrofti) in American soldiers. *Am. J. M. Sc.* 210: 507-511, 1945.
- Rush, A. Anxiety neuroses manifested by gastro-intestinal symptoms. *M. Clin. North America* 28: 1541-1553, 1944.
- Idem. Fractional gastric analysis: simplified technique with interpretation of results. *M. Clin. North America* 28: 1516-1526, 1944.
- Denhoff, E. Hematologic values in American soldiers stationed in the tropics. *J. Lab. & Clin. Med.* 30: 874-882, 1945.
- Belding, D. L. *Textbook of Clinical Parasitology Including Laboratory Identification and Technique*. 888 pp. New York: D. Appleton-Century Company, 1942. P. 792.
- Strong, R. P. *Shi's Diagnosis, Prevention and Treatment of Tropical Diseases*. Sixth edition. 2 vol. 1747 pp. Philadelphia: Blakiston Company, 1943. Vol. 2 P. 1270.
- Allen, H. C. Eosinophilia in South Pacific. *U. S. Nav. M. Bull.* 4: 1241-1244, 1944.
- Chacon, A. L. *The Clinical Symptomatology of Ankylostomiasis*. United Fruit Company Medical Department, Twentieth Annual Report, 1931. Pp. 176-178.
- Rogers, A. M., and Dammann, G. J. Hookworm infection in American troops in Assam and Burma. *Am. J. M. Sc.* 211: 531-538, 1946.
- Gradwohl, R. B. H. *Clinical Laboratory Methods and Diagnostic Procedures*. A textbook on laboratory procedures with their interpretation. 10th edition. Vol. 1. 1076 pp. St. Louis: C. V. Mosby Company, 1943. P. 838.
- Wagner, E. A. *Strongyloides stercoralis*. *Ohio State M. J.* 32: 325-329, 1936.
- Faust, E. C. Symptomatology, diagnosis and treatment of strongyloid infection. *J. A. M. A.* 98: 2276, 1932.
- Fidler, A., Innes, J., and Davidson, L. Duodenal intubation and significance of cellular content of bile in diagnosis of diseases of biliary tract. *Brit. M. J.* 2: 865-869, 1941.

is has been given to this trend by the anatomical lies of the lymphatic drainage areas carried out Dukes,³² Grinnell,³³ Kay³⁴ and others. Their findings establish that downward lymphatic spread in rectal cancer is rare and only likely to occur in the upward-draining lymphatic vessels are clogged by cancer metastases. These conservative operations are technically difficult and probably no so sound as the more orthodox procedures from the point of view of a thorough operation. The likelihood of postoperative complications appears to be greater, and the prospect of adequate function of the preserved sphincter is problematical. In addition, whereas the procedures perhaps fulfill the requirement so far as lymph-node involvement is concerned, they appear to disregard the fact of venous involvement, which is increasingly recognized as significant.

An important study of carcinoma of the rectum on a state-wide basis has recently been presented by Ottenheimer,³⁵ who reports the experience in Connecticut. The value of such a survey cannot be overemphasized. It serves both to define the problem and to provide a base line against which progress can be measured. Although other states may plead the increased difficulties of such surveys in a heterogeneous population, the value of this approach to cancer of various regions is obvious. It is to be hoped that further studies on other groups will be carried out.

Carcinoma of the Cervix

The Papanicolaou³⁶ test for cancerous cells in the vaginal smears has been hailed with some enthusiasm as a method of screening patients to find carcinoma of the uterus in a presymptomatic stage. In the hands of competent interpreters of the slides it may achieve a high degree of accuracy. The method has been applied to other secretions, such as sputums, gastric washings and the contents of cysts. It may prove to be a useful adjunct to diagnostic procedures. It is probably too protracted and too dependent on expert interpretation for use as a routine screening procedure on a large completely asymptomatic group of patients.

Meigs³⁷ has continued his series of Wertheim operations in selected cases of carcinoma of the cervix. In the cervix, as in the larynx, radical surgery in selected cases yields excellent results. Radical radiation is also extremely effective, especially in early cases, whereas the selection of cases is not nearly so exacting. Here, as in the larynx, certain cases are refractory to radiation, and it is desirable to attempt more accurate identification of this refractory group. Taussig's³⁸ operation of iliac lymphadenectomy — a retroperitoneal dissection of the lymph-node areas — was designed to take care of lymph-node metastases following destruction of the primary cancer by radiation. Taussig found involved nodes in about 40 per cent of the patients sub-

mitted to the operation, in whom he obtained cures in about 25 per cent. Recently, Nathanson³⁹ accomplished the same objective by means of a retroperitoneal dissection through bilateral incisions in the groins.

Lymphoblastoma

The definitive classification of the lymphoblastomas was presented by Jackson and Parker.⁴⁰ Formerly, the terminology had been confusing, and it was often difficult to decide which group of tumors was under discussion in studies from various clinics. The work of Jackson and Parker, with its wealth of pathological material correlated with clinical progress, should lay the groundwork for appropriate therapeutic efforts.

Bone Tumors

In recent years, the clinician concerned with the diagnosis of bone disease has had to learn to recognize osteoid osteoma⁴¹ and eosinophilic granuloma.⁴² Although neither of these tumors is a true neoplasm, their occurrence and identification has probably added another difficulty to an already confusing problem. Fortunately, both lesions are benign and respond readily to appropriate surgical measures.

Carcinoma of the Prostate

Although Huggins⁴³ first reported his experiences in the treatment of carcinoma of the prostate by orchiectomy and estrogens several years ago, the literature still contains reports of successes, and there is some question regarding the duration of the remissions and the types of the disease likeliest to respond favorably. It is probable that several more years will elapse before final appraisal of this undoubtedly valuable adjunct of treatment.

Radiation Therapy

Holmes and Schulz⁴⁴ have published the results of million-volt x-ray therapy. They found less skin damage from the dose delivered to the tumor than with lower voltages. The results of treatment appear to be superior in carcinoma of the bladder,⁴⁵ cervix, lung and tonsil.

Miscellaneous

Pack and Ehrlich⁴⁶ published techniques as well as a series of cases of radical amputations, including the shoulder girdle, hip joint and sacroiliac. These mutilating procedures are occasionally indicated in extensive malignant processes, and as the authors point out, they may be indicated for palliation in some cases.

The criteria of malignancy have already been referred to in the discussion of thyroid carcinoma. The clinician is too ready to accept as fact the diagnosis offered by the pathologist without recognizing that such a diagnosis is a conclusion and judgment based on an assembly of data. One is occasionally

Thus, the operation is essentially a radical neck dissection except that the submaxillary area need not be included. The likelihood of lymph-node metastasis as the sole or earliest manifestation of spread is great, especially in the relatively low-grade papillary adenocarcinomas.

Lahey¹¹ has again emphasized the likelihood of the development of malignant changes in aberrant thyroid nodules. It must be recognized that some tumors of this sort may be metastases from undetected primary foci of disease in the thyroid gland itself.

The use of thiouracil in the treatment of hyperthyroidism involves some consideration of its possible relation to carcinogenesis in the gland. Bielschowsky¹² reported the development of cancer of the thyroid gland in experimental animals by the use of a carcinogen, 2-acetyl-amino-fluorene, in conjunction with allyl-thiourea. Neither compound alone was capable of producing thyroid carcinoma in control animals.

Carcinoma of the Breast

Foote and Stewart¹³ have made a major contribution to the pathology of benign breast conditions and their relation to carcinoma. Haagensen and Stout¹⁴ reported an exhaustive analysis of their experience with carcinoma of the breast, especially analyzing the prognostic significance of certain clinical manifestations of the disease. Their experience was closely paralleled by that of Wells¹⁵ and, indeed, coincides with that of most other clinics where a considerable number of these patients are treated. Variations in the criteria of operability probably account for variations in results. The use of estrogens in the treatment of advanced carcinoma of the breast, especially in patients beyond the age of sixty, promises to be a valuable palliative procedure in some cases.^{16, 17} It is too early to discover how long the regressions may be maintained. The use of testosterone has also brought about regressions in certain cases.¹⁸

Carcinoma of the Lung

Tremendous strides have been made in recent years in the technics of thoracic surgery, and significant series of radical operations for lung carcinoma are now recorded. Lindskog¹⁹ called attention to the low operability rate for radical procedure and the advanced stage of disease presented by most patients when first seen. Mass screening by chest x-ray examination, which has successfully been carried out for tuberculosis, might be applied to a large group in an attempt to find cancer of the lung in a presymptomatic and favorable stage. Herbut and Clerf²⁰ have applied the Papanicolaou method of examination to sputums, with encouraging results.

Carcinoma of the Esophagus

In no field has the development of thoracic surgery led to such rapid progress as in the problem of carcinoma of the esophagus and of the cardiac end of the stomach. Sweet²¹ has reported a brilliant series of esophageal resections, with a constantly diminishing mortality. It is discouraging to discover that lymph-node metastases are frequent, occurring early, and that attempts to include many of them in the resection are not successful. Even as a palliative procedure, however, the operation is highly successful. A similar approach and technique give excellent access to carcinomas at the cardiac end of the stomach, in which the results are also promising.²²

Carcinoma of the Stomach

As in carcinoma of the lung, a discouraging picture applies to carcinoma of the stomach in the fact that operability rates for radical excision remain relatively low. Wangenstein²³ and his co-workers undertook screening by gastric analysis, followed by further investigation of the achlorhydric patients. In this fashion they found a significant number of patients with gastric polyps, which are often conceded to be precancerous. Various authors^{24, 25} have extended the indications for radical surgery in most abdominal carcinomas to include a large group with fixation to adjacent organs and with metastases in the liver and spleen. Although these operations are a challenge to surgical skill and to the restorative and antishock efforts of the team, it is doubtful whether much good is accomplished, even as palliation.

Carcinoma of the Pancreas

The development of the Whipple²⁶ operation and its various modifications have made it possible to attack carcinomas of the pancreas,²⁷ duodenum and bile ducts²⁸ with greater assurance, lessened operative mortality and an increased likelihood of success. These advances are due not only to technical progress but also to improved understanding of maintenance of physiologic equilibrium.

Carcinoma of the Colon and Rectum

In recent years a revived employment of open resections in the colon has been made possible in part by improvements in technic and in part by the use of decompression as a safeguard, as well as by the use of chemotherapeutic agents, especially sulfa-thalidine and succinylsulfathiazole (Sulfasuxidine). The increased safety of open resections has led to revival of procedures to preserve the anal sphincter and to avoid a permanent colostomy in dealing with growths that are low in the colon.²⁹⁻³¹ Some of

SE RECORDS OF THE SSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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EDITH E PARRIS, *Assistant Editor*

CASE 33061

PRESENTATION OF CASE

First admission A forty-three-year-old automobile aler was admitted to the hospital because of chest in

On the previous day the patient had suddenly en seized with pain beneath the sternum and upper ick, noted especially on deep breathing. The pain rsisted, growing worse when he was lying down, id kept him awake for a time, although he felt etter on the following day. Work intensified the ain, especially when he stooped. He visited a ysician, who found no fever, hoarseness or pharyn- eal congestion, but because of a white-cell count of 3,000 he was referred to the hospital.

The patient had had two gonorrheal infections he second one occurring three years previously both had cleared with therapy. He smoked con- tantly and took small amounts of alcoholic drinks egularly.

Physical examination revealed that the heart was ot enlarged and that the sounds were of good qual- ty. Nothing else of note was found.

The pulse was 110, and the blood pressure 150 systolic, 90 diastolic.

Examination of the blood showed white-cell counts of 9000 and 12,500, with normal differential counts. The urine was normal. X-ray examination of the chest was negative. An electrocardiogram dis- closed rather low QRS complexes in Leads 1, 2 and 3 but normal ST segments and T waves in all four leads. The patient was discharged two days after admission.

Second admission (two years later) The patient had had no further symptoms since the previous ad- mission until he was again admitted for chest pain. About 1 00 a m on the day before admission the patient awoke with an aching substernal pain pen- etrating to the back and spreading to both shoulders and down both arms. He arose and stayed up the rest of the night. The pain lessened during the next day but persisted beneath the xiphoid and extended to the throat. Lying on the back eased it only slightly and sitting up or lying on either side made it worse.

Physical examination revealed a split aortic second sound along the left sternal border but no enlarge- ment of the heart or other abnormalities.

The temperature was 100°F.

Examination of the blood disclosed a white-cell count of 21,900, with 95 per cent neutrophils, with a shift to the left. The hemoglobin was 16.5 gm. The urine was normal except for a ++ test for al- bumin and 150 white cells per high-power field in the sediment. An x-ray film of the chest revealed a moderately enlarged heart with prominence in the region of the left ventricle. Fluoroscopically the pulsations were weak. The aorta was somewhat tortuous, without evidence of dilatation. The lung fields were clear except for a small area of increased density in the right base. A barium swallow showed a small hiatus hernia. An electrocardiogram revealed normal rhythm and a rate of 95. There was high origin of the T waves in Lead 1, with moderate late inversion, a flat T₂ and a diphasic T₃. The QRS complexes were low in the limb leads, and the pre- cordial leads showed an absent upright R wave in Leads CF₂ and CF₄, with high origin of the ST in- tervals in Leads CF₂ and CF₄, and late inversion of the T waves.

By the second hospital day the pain had dis- appeared and did not recur even on deep inspiration. Examination of the blood showed a white-cell count of 13,200. A gastrointestinal series revealed redun- dancy of the duodenum between the first and second portions. An electrocardiogram four days after ad- mission showed a slight change in the appearance of the ST intervals. ST₁ appeared more elevated, and T₁ was definitely inverted. ST₂ was more depressed, and in the precordial leads there was more elevation of the ST intervals and less late inversion. After two weeks the patient was transferred to a convalescent hospital, where he remained for three weeks.

Final admission (four months later) The patient returned to the hospital because of recurrent pain in the chest. Following discharge he had restricted his activity for a while and had then gone for short walks. He was able to climb three flights of stairs without difficulty, and during the third week he tried a short period of work at the office. That night, however, he had a severe attack of precordial pain radiating to both arms and to the back. He was seen by a physician, who observed a blood pressure of 150 systolic, 100 diastolic, and an apical gallop rhytm. The pain lasted for two days, and the patient remained in bed until a week before admis- sion, when he was allowed to sit in a chair. He occa- sionally developed some swelling of the ankles while sitting up. At 4 00 a m on the day of admission he had another attack of substernal pain, without radiation, but exaggerated on deep breathing.

Physical examination showed the patient to be in moderate discomfort, with steady substernal pain. The heart was moderately enlarged. The pulse was 96, with multiple extrasystoles. Crackling rales were heard at the left base, and the neck veins were prominent. The blood pressure was 104 systolic, 74 diastolic.

confronted with tumors whose clinical behavior is at variance with their histologic character. It is for this reason that great interest centers on the work of Greene and Lund,⁴⁷ who succeeded in growing human malignant tumors in the anterior chamber of the guinea-pig eye. This capacity for growth is apparently not shared by benign tumors, and the procedure may prove of value in determining the nature of a tumor in which the histologic character is obscure or equivocal.

264 Beacon Street

REFERENCES

- 1 Martin, H. E. Treatment of cervical metastatic cancer. *Ann Surg* 114 972-985 1941
- 2 *Idem*. Cancer of gums (gingival). *Am J Surg* 54 765-806 1941
- 3 Taylor, G. W. and Nathanson, I. T. *Lymph Node Metastases: Incidence and surgical treatment in neoplastic disease*. 498 pp. New York: Oxford University Press, 1942
- 4 Cutler, M. Concentrated radiotherapy of cancer: study of 413 cases. *J A M A* 124 967-976 1944
- 5 Schall, L. A. Carcinoma of larynx. *New Eng J Med* 229 574-576, 1943
- 6 McFarland, J. Mysterious mixed tumors of salivary glands. *Surg, Gynec & Obst* 76 23-34 1943
- 7 Bickham, W. S. *Operative Surgery: Covering operative technique involved in operations of general and special surgery*. Vol. 7. 849 pp. Philadelphia: W. B. Saunders Company, 1924
- 8 McCormack, L. J., Cauldwell, E. W., and Anson, B. J. Surgical anatomy of facial nerve with special reference to parotid gland. *Surg, Gynec & Obst* 80 620-630 1945
- 9 Cole, W. H., Slaughter, D. P., and Rossiter, L. J. Potential dangers of nontoxic nodular goiter. *J A M A* 127 883-888, 1945
- 10 Rawson, R. Personal communication
- 11 Lahey, F. H., Hare, H. F., and Warren, S. Carcinoma of thyroid. *Ann Surg* 112 977-1005, 1940
- 12 Bielschowsky, F. Tumours of thyroid produced by 2-acetyl amino-fluorene and allyl thiourea. *Brit J Exper Path* 25 90-95 1944
- 13 Foote, F. W. and Stewart, F. W. Comparative studies of cancerous versus noncancerous breasts. *Ann Surg* 121 6 and 197 1945
- 14 Haagensen, C. D., and Stout, A. P. Carcinoma of breast: criteria of operability. *Ann Surg* 118 1032-1051 1943
- 15 Wells, D. Unpublished data
- 16 Haddow, A., Watkinson, J. M., and Paterson, E. Influence of synthetic oestrogens upon advanced malignant disease. *Brit M J* 2 393-398, 1944
- 17 Nathanson, I. T. Effect of stilbestrol on advanced cancer of breast. *Cancer Research* 6 484 1946
- 18 Adair, F. E., and Hermann, J. B. Use of testosterone propionate in treatment of advanced carcinoma of breast. *Ann Surg* 123 1023-1035 1946
- 19 Lindsag, G. E. Bronchiogenic carcinoma. *Ann Surg* 124 667-674, 1946
- 20 Herbut, P. A., and Clerf, L. H. Bronchiogenic carcinoma: diagnosis by cytologic study of bronchoscopically removed secretions. *J A M A* 130 1006-1012 1946
- 21 Sweet, R. H. Transthoracic resection of esophagus and stomach for carcinoma: analysis of postoperative complications, causes of death and late results of operation. *Ann Surg* 121 272-284 1945
- 22 Phemister, D. B. Transthoracic resection for cancer of cardiac end of stomach. *Arch Surg* 46 915-929 1945
- 23 Wangensteen, O. H. Unpublished data
- 24 Brunschwig, A., and Morton, D. R. Resection of abdominal carcinomas involving liver and spleen secondarily. *Ann Surg* 131 746-754 1946
- 25 Sugarbaker, E. D. Coincident removal of additional straddled resections for carcinoma of colon and rectum. *Ann Surg* 131 1036-1046 1946
- 26 Whipple, A. O. Present-day surgery of pancreas. *New Eng J Med* 226 515-526, 1942
- 27 Brunschwig, A. Surgical treatment of carcinoma of body of pancreas. *Ann Surg* 120 406-416 1944
- 28 Pickrell, L. L., and Blalock, A. Surgical treatment of carcinoma of common bile duct. *Surgery* 15 923-937, 1944
- 29 Wangensteen, O. H. Symposium on surgical management of malignancy of colon: primary resection (closed anastomosis) of cecum and rectosigmoid including description of abdomino-anal anastomosis for restoration of continuity accompanying excision of carcinoma of rectal ampulla. *Surgery* 14 403-432, 1943
- 30 Dixon, C. F. Anterior resection for carcinoma low in sigmoid: rectosigmoid. *Surgery* 15 367-377, 1944
- 31 Bacon, H. E. Evolution of sphincter muscle preservation and re-establishment of continuity in operative treatment of rectal and sigmoid cancer. *Surg, Gynec & Obst* 81 113-127 1945
- 32 Dukes, C. J. Surgical pathology of rectal cancer. *Proc R Soc Med* 37 131-144, 1944
- 33 Grinnell, R. S. Lymphatic and venous spread of carcinoma of rectum. *Ann Surg* 116 200-216, 1942
- 34 Kay, E. B. Regional lymphatic metastases of carcinoma of gastrointestinal tract. *Surgery* 12 553-562 1942
- 35 Ottenheimer, E. J. Unpublished data
- 36 Papanicolaou, G. N., and Marchetti, A. A. Use of endometrial and endometrial smears in diagnosis of cancers and of other conditions of uterus. *Am J Obst & Gynec* 46 421, 1943
- 37 Meigs, J. V. Wertheim operation for carcinoma of cervix. *Am J Obst & Gynec* 49 542-553 1945
- 38 Taussig, F. J. Iliac lymphadenectomy for group II cancer of cervix: technique and five-year results in 175 cases. *Am J Obst & Gynec* 73 733-748 1943
- 39 Nathanson, I. T. *Progress in Gynecology*. Edited by J. V. Meigs and S. H. Sturgis. New York: Grune and Stratton, 1946
- 40 Jackson, J., Jr., and Parker, F. Jr. Hodgkin's disease. II. Pathology. *New Eng J Med* 231 35-44, 1944. III. Symptoms and course. *Ibid* 231 639-646, 1944. IV. Involvement of certain organs. *Ibid* 232 547-559 1945. V. Involvement of certain other organs. *Ibid* 233 369-378 1945. VI. Clinical diagnosis. *Ibid* 234 37-41 1945. VII. Treatment and prognosis. *Ibid* 234 103-110, 1946.
- 41 Jaffe, H. L. Osteoid-osteoma of bone. *Radiology* 45 319-334, 1945.
- 42 Solomon, H. A., and Schwartz, S. Eosinophilic granuloma of bone. *J A M A* 128 729-731 1945
- 43 Huggins, C. Endocrine control of prostatic cancer. *Surgery* 5 541-544 1943
- 44 Holmes, G. W., and Schulz, M. D. Supervoltage radiation therapy of cases treated during eight year period (1937-1944) inclusive. *Am J Roentgenol* 55 533-554 1946
- 45 Colby, F. H., and Schulz, M. D. Review of carcinoma of blood treated by supervoltage x rays over five-year period. *Radiology* 4 371-377, 1943
- 46 Pack, G. T., and Ehrlich, H. E. Exarticulation of lower extremity for malignant tumors: hip joint disarticulation (with and without deep iliac dissection) and sacro-iliac disarticulation (hemipelvectomy). *Ann Surg* 123 965-985 and 124 1-27, 1946
- 47 Greene, H. S. N., and Lund, P. K. Heterologous transplantation of human cancers. *Cancer Research* 4 352-363 1944

gesting that the use of anticoagulants in patients who are having recurrent episodes of coronary thrombosis inhibits to some extent the formation of further coronary thrombi. I should be less hopeful, perhaps, about preventing these recurring episodes by this form of therapy than of lessening the chances of complications. In this connection, a report last summer in the *Journal of the American Medical Association*² recorded a series of 110 cases of acute myocardial infarction, 60 of these patients were used as controls and 50 were given anticoagulant therapy in the form of dicumarol. Of the control group 16 per cent developed clinically manifest peripheral emboli, and only 2 per cent of the treated group developed clinical embolism. That is a significant difference. Furthermore the deaths in the treated group were much fewer than those in the untreated group. This problem obviously requires extensive study and observation, preferably by more than one clinic or one group. Therefore, the American Heart Association has embarked on a project to study a large number of cases in several clinics under a controlled program so that each investigator will more or less follow the same scheme. The present arrangement is to treat alternate cases of acute myocardial infarction with anticoagulant therapy, such a program is now in progress in this hospital, as well as in several large hospitals elsewhere in this country. The answer remains to be seen.

What are the possible disadvantages of this therapy? A large mural thrombus might serve as a slow-out patch to prevent actual rupture of the heart. If the stoutness or extent of the thrombus is lessened, more cases of rupture of the heart may theoretically be expected. Perhaps Dr Mallory will express an opinion on that score. Furthermore, I have discussed with the surgeons what their reaction would be to a patient in whom, in spite of dicumarol therapy, a femoral artery suddenly occluded. Would they hesitate to do an embolectomy? They have not yet encountered this situation, but operation would not be contraindicated in spite of a prothrombin time between 35 and 50 seconds, which is the effective therapeutic level. There is one further probable indication for anticoagulant therapy in acute myocardial infarction: irritability of the heart with paroxysms of auricular fibrillation which, as is well known, is prone to result in thrombosis in the auricle and embolism peripherally.

In conclusion, it seems that this case afforded an ideal situation for this new and special form of therapy. We believe that it is reasonably safe. Before Dr Mallory tells us the post-mortem findings, I think that the clinical record should be clear. It is implied but not definitely stated that the patient was kept on dicumarol up to the time of death.

DR JAMES H. CURRENS That is correct.

DR BLAND We therefore have an opportunity in this case to see what thrombotic phenomena were

present after a patient had been on dicumarol for three months. I know of one patient kept on anticoagulant therapy for a period of six months without untoward effects.

DR JAMES H. TOWNSEND Would you predict where the various infarcts were?

DR BLAND That would lead us into a somewhat detailed discussion in this case.

DR TOWNSEND Which one occurred in which of these admissions?

DR BLAND In the second episode the electrocardiogram, as I have previously stated, was characteristic of an infarct in the region of the apex. The subsequent changes in the electrocardiogram with the third episode were rather noncommittal, suggesting further injury in the same region, or perhaps the electrocardiogram was modified either by the use of digitalis or by an infarct at the base. I should prefer not to go into great detail on that point. I think that the major infarct was at the cardiac apex. I should not be surprised if there were multiple infarcts in the heart, some large and some small, or if autopsy showed some old scars in the lung, possibly healed pulmonary infarcts.

DR BENJAMIN CASTLEMAN What do you think was the cause of death?

DR BLAND The patient died suddenly, as many patients with severe coronary disease do. I wondered perhaps if the heart had ruptured at the end. If it did, one must presuppose a fresh myocardial infarct, because healed infarcts do not rupture. The only clue was the two-week period of angina pectoris near the end, which may have represented further softening in the myocardium. In most people who die suddenly with coronary disease, however, we find simply marked coronary narrowing with areas of old infarction and occasionally a tiny fresh clot in one of the chronically obstructed coronaries, but usually not enough time elapses for microscopical or gross infarction to become evident. Many patients in the presence of marked coronary disease succumb suddenly, and we are unable to determine any specific additional cause of death at that particular moment. Perhaps it is cardiac standstill or ventricular fibrillation. Was quinidine given to this patient?

DR CURRENS No.

DR BLAND Was digitalis given?

DR CURRENS I believe that it was.

DR BLAND I shall be surprised if Dr Mallory says that the patient had a ruptured heart. I suspect that no specific cause for the final exitus, other than extensive coronary disease, was found.

DR CASTLEMAN In the new project, how long is a patient kept on anticoagulant therapy?

DR BLAND Six weeks. This project has just started. I do not know the laboratory details. Only one patient has been treated, and he died on the

Examination of the blood revealed a hemoglobin of 14.5 gm and a white-cell count of 20,400, with 84 per cent neutrophils and a shift to young forms. The urine showed a + test for albumin, and the sediment contained 20 white cells per high-power field. An electrocardiogram showed normal rhythm at a rate of 100, interrupted by ventricular premature beats. The QRS complexes were low in the limb leads. The T waves were flat in Lead I and low but diphasic in Leads 2 and 3, the PR interval was 0.18 second. The precordial leads showed inverted QRS complexes in Leads CF₁ and CF₂, with upright T waves and a flat T wave in Lead CF₄.

Anticoagulant therapy with dicumarol was instituted, and the prothrombin time was maintained at an average of approximately 40 seconds, with a control of about 18 seconds. The patient showed improvement during the first ten days of hospitalization, but subsequent electrocardiograms revealed slightly higher voltage in the limb leads and more inverted T waves in Leads I and CF₁. On the morning of the twenty-first hospital day, as on previous mornings, he complained of a sensation of "fluttering" and of "water" rushing through the precordial region but no pain. On physical examination the rhythm was grossly irregular, characteristic of fibrillation, but this changed shortly to a normal sinus rhythm, with frequent extrasystoles every third to fifth beat. The rate was about 92. He was discharged on that day.

The patient continued to take dicumarol, with frequent checks of the prothrombin time, which maintained an average of 40 to 50 seconds. After several weeks of rest in bed he gradually resumed physical activity and even returned to his office part time, but found it increasingly difficult to adapt himself to the disease. He became depressed, began to drink liquor freely, and had mild anginal attacks for two weeks. He died suddenly about three months after discharge.

DIFFERENTIAL DIAGNOSIS

DR EDWARD F. BLAND: We need spend little time in the discussion of the differential diagnosis, since it is obvious that the relatively new method of treatment employed in this case is the point of chief interest. Attention might be called, however, to the first episode of pain at the age of forty-three. The diagnosis in that attack from the clinical description is a little uncertain. The trouble was most probably of coronary origin, it could have been a pulmonary infarct. The pain was steady, and breathing caused discomfort. It is slightly unusual for the pain of a myocardial infarct to be sharply accentuated by breathing. That observation usually points to the lung, pleura or pericardium. There was no proof of a pulmonary infarct by x-ray examination or of a myocardial infarct on the electrocardiograms. The clinicians apparently did not consider this a serious illness, because the patient was per-

mitted to return home the next day. The subsequent course supported their decision, because there was no further trouble for two years.

The second episode, at the age of forty-five, was clearly, I believe, a coronary occlusion. The character of the pain radiating down both arms and the characteristic findings in the electrocardiogram pointing to a myocardial infarct at the apex of the heart leave little doubt regarding the diagnosis. The fact that the blood pressure did not drop need not be considered because when patients are seen during the course of coronary thrombosis — if they are having pain and if vascular shock has not occurred — the pressure is likelier to be elevated than the reverse. Furthermore, there was some enlargement of the heart. The statement in the x-ray report of slight density at the right base raises the possibility of a complicating pulmonary infarct. I shall ask Dr. Schatzki about that later.

DR RICHARD SCHATZKI: There are no x-ray films.

DR BLAND: We might proceed then to the third episode of pain, which was severe enough to cause the patient to come to the hospital. At that time he had signs of heart failure. The electrocardiogram showed changes from the previous record, but it must be remembered that he was probably taking digitalis, although it is not so stated in the record. I believe that this episode was also caused by myocardial infarction.

A fourth attack of severe pain, which occurred in the hospital, could have been due to a pulmonary or a myocardial infarct, most probably the latter. From this sequence of events I believe that there is no doubt that this man was suffering from severe coronary heart disease, with recurring episodes of myocardial infarction and possibly occasional pulmonary infarcts, and that he ultimately died abruptly in a manner characteristic of severe coronary disease.

Let us pass to the therapy, which introduces, I suspect, the real reason for bringing up this case — namely, the use of anticoagulants under these circumstances. During the past year there have been three reports in the literature concerning the use of anticoagulant therapy following acute myocardial infarction. The evidence is suggestive that such a procedure may be helpful in inhibiting complications. Statistics reported by Barker¹ indicate that following an acute myocardial infarct there is approximately a 35 per cent chance that patients within the first six weeks will have some form of thromboembolic complication, if one includes both peripheral thrombophlebitis and pulmonary infarcts, as well as thrombi in the heart and consequent peripheral emboli. Actually that figure seems too high to me. Nevertheless, the risk of such complications is considerable. In the face of this, anticoagulant therapy seems rational to prevent these thromboembolic complications. Furthermore, there has been at least one report mentioned by Barker¹

lized, midabdominal pains, but the bowels moved. A questionable mass was palpated in the lower quadrant. A month later the bowels were sluggish, and there was some distention but no pain. Seven months before admission an occasional, mild abdominal pain occurred. The abdomen was soft. A month before admission the bowel movements were loose, and there had been increasing anorexia and a weight loss of 10 to 15 pounds. Three weeks before admission barium-enema study was negative except for marked dilatation of the cecum and the ascending and the transverse colon. The distention became more persistent, and during the week before admission frequent enemas were required for relief, although the bowel movements were spontaneous and normal. The patient vomited small amounts once or twice daily. Four days before admission a colonic irrigation gave considerable temporary relief.

Some years before the present illness an appendectomy had been followed by a phlebitis in the right leg. There had been attacks of mild cystitis, one, two and one year before admission, each lasting from a week to a day. Ten years before admission the pelvis had been fractured in an automobile accident.

Physical examination disclosed an obese patient who nevertheless showed signs of weight loss. The abdomen was distended, soft and nontender. Peristalsis was increased. No mass was felt. There were external hemorrhoids. Rectal examination was negative.

The temperature was 98.2°F, the pulse 88, and the respirations 20. The blood pressure was 140 systolic, 80 diastolic.

Examination of the blood revealed a hemoglobin of 14.2 gm and a white-cell count of 9700, with 32 per cent neutrophils. The urine was normal. No ova, parasites or red cells were found in the stools on repeated examination. The stools were guaiac negative. A barium enema revealed an area of rather marked narrowing in the middle and upper sigmoid over a distance of approximately 12 cm. The lumen was irregular, and in the midportion there was an uneven area that could have represented a pocket extending beyond the bowel lumen. There were a few diverticula in the distal sigmoid, but none in the region of the narrowing. The margins of the latter were not shelved. Barium passed beyond the obstruction showed considerable fecal material in the dilated colon. The small bowel was also dilated. Fluoroscopically there was thought to be a shadow behind the heart, possibly a hernia, but this did not contain colon.

On the second hospital day, proctoscopic examination was negative up to 15 cm above the anus. The patient's condition continued unchanged for nine days, when a cecostomy and a prophylactic bilateral femoral-vein ligation were performed. The postoperative course was satisfactory. The

colon was drained by a Miller-Abbott tube inserted through the cecostomy. The small-bowel distention gradually decreased but did not disappear. The urinary output, which was low for two days, subsequently increased. The serum protein had dropped to 3.6 gm per 100 cc by the fifth postoperative day. The white-cell count reached a maximum of 16,000 on one occasion, a transfusion with 500 cc of blood was given at the time of operation, and again on the fifth postoperative day. On the twenty-third hospital day a second operation was performed.

DIFFERENTIAL DIAGNOSIS

DR FRANCIS D MOORE This woman in the seventh decade of life, after six years of vague abdominal rumbling, which presaged further trouble, developed abdominal symptoms in a gradual crescendo that reached a maximum at the time of admission, when the previous, rather vague and intermittent symptomatology yielded to symptoms of obstruction with anorexia and weight loss. The significant items of that six-year history are the duration and the finding, a year before admission, of diverticulosis with spasm in the sigmoid, justifying a diagnosis of diverticulitis. This bout of difficulty had evidently subsided spontaneously, only to recur on various occasions prior to admission, the most recent episode taking the form of an intensified version of the previous ones.

The past history does not cast a great deal of light on the present symptoms except that, since the appendix had been removed, we presumably need not worry about that as a source of the present trouble.

On physical examination, the patient was noted to be obese, which as I shall point out later is probably significant. Examination of the abdomen showed low-grade, large-bowel obstruction. The patient was not systemically ill and had little evidence on physical or laboratory examination of invasive infection. The negative guaiac test was of course of great interest and probably significant, although it would be nice to know whether multiple tests were carried out. The x-ray findings, needless to say, are of the greatest importance.

X-ray study revealed narrowing, with neighboring diverticulosis. We need not waste time on the well known fact that the diverticula involved in acute diverticulitis often do not show in the x-ray film, owing to the fact that they are filled with purulent material, to edema of the mucosa or to fecal material, or to a combination of the three. The significant facts are that the margins of the defect were not shelved and that some obstruction was produced. Dilatation of the small bowel simply indicates that the ileocecal valve was not competent. The negative proctoscopic examination is of little help one way or another, since the patient's lesion was well above 15 cm from the anus. The lack of

third day, he had a massive myocardial infarct. We have not yet had enough experience with this new project to make definite statements.

CLINICAL DIAGNOSIS

Coronary thrombosis, recurrent, with myocardial infarction

DR. BLAND'S DIAGNOSES

Coronary heart disease
Myocardial infarcts

ANATOMICAL DIAGNOSES

Coronary sclerosis, severe
Myocardial infarcts, anterior, old, and posterior, recent
Pulmonary congestion and edema
Horseshoe kidney

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: Post-mortem examination showed a considerably hypertrophied heart, which weighed 550 gm. All the branches of the left coronary artery were markedly sclerotic and partially calcified with fibrous narrowing. There were, however, minute pin-point lumens suggesting that thrombi had been recanalized. No acute change was found in the coronary arteries to explain why this man died at the particular moment that he did. The left ventricle showed two definitely separable areas of infarction. One on the anterior surface, well toward the apex, was very old and fibrous. The second one, which was found on the posterior surface and slightly toward the base, was also of considerable duration — some weeks at least. It was probably responsible for the third episode. The endocardium over both infarcts was thickened and sclerotic, but there were no fresh thrombi. The lungs showed marked congestion, indicating that there had been sudden left ventricular failure, which must have lasted for a few minutes before death.

The only other finding was an anatomical curiosity, a horseshoe kidney which I am sure had no significance.

On microscopic examination the liver showed a rather extensive fatty vacuolization — more than could be accounted for by heart failure — but could be explained by the alcohol to which the patient turned for consolation during the last few months of life. It had not progressed far enough, however, to produce any degree of liver insufficiency.

DR. CURRENS: One or two features of the clinical course were interesting. In a period of four months the patient had four episodes of pain entirely consistent with the diagnosis of coronary thrombosis. Because of these recurrent attacks, it was decided to place him on dicumarol therapy. He was certainly a suitable patient to follow for a time. All

four attacks of pain appeared at night, awaking him from a sound sleep. The blood pressure was found to be quite low, particularly in the morning, the diastolic pressure being 50 and the systolic 80 to 90. At the time of the pain, however, the arterial blood was able to constrict and produce moderate hypertension.

So far as dicumarol therapy is concerned, it was easy to carry him and maintain a prothrombin level between 20 and 40 per cent with 15 mg. of the drug after the initial dicumarolization. The dosage varies tremendously from patient to patient, and the individual daily dosage must be established if one decides to carry it over that length of time. The fact that there was no evidence of recent infarction or thrombosis may be significant.

DR. BLAND: It is also significant that the lungs were clear so far as pulmonary emboli were concerned.

Were the peripheral vessels examined?

DR. MALLORY: They were not examined, since we found no infarction in the lung.

Whenever a new drug is introduced the pathologist naturally looks for manifestations of toxicity. The only evidence of dicumarol toxicity described to date is extensive hemorrhage with uncontrolled dosage.¹ Patients have died with subarachnoid, gastrointestinal and renal hemorrhages. There was no manifestation in this case that could have been considered evidence of toxicity.

REFERENCES

1. Barker, N. W. Anticoagulant therapy [*Mod. Concepts Cardiovasc. Dis.* 15 No. 11, 1946].
2. Peters, H. R., Guyther, J. R., and Bramble, C. E. Dicumarol in acute coronary thrombosis. *J. A. M. A.* 130 398-403, 1946.
3. Shlevin, E. L., and Lederer, M. Uncontrollable hemorrhage after dicumarol therapy, with autopsy findings. *Ann. Int. Med.* 21 332-342, 1944.

CASE 33062

PRESENTATION OF CASE

A sixty-seven-year-old housewife entered the hospital because of recurrent abdominal distention and pain.

Six years before admission the patient had had a single attack of abdominal pain, without diarrhea, for which no explanation was found. Five years later an attack of distention, with fever, constipation and abdominal distress, occurred. A plain film of the abdomen showed a large amount of gas and fecal matter distending the colon. The barium enema reached nearly to the splenic flexure. The whole descending colon was distended with feces and the patient was unable to retain the enema. There was considerable spasm in the sigmoid, and a few diverticula were seen. With colonic irrigation and mineral oil by mouth the symptoms ceased, only to recur again in ten days. Examination of the abdomen was negative except for distention, which cleared after a day or so. Eleven months before admission, the patient was having colicky, non-

lized, midabdominal pains, but the bowels moved. A questionable mass was palpated in the lower quadrant. A month later the bowels were sluggish, and there was some distention but no pain. Seven months before admission an occasional, mild abdominal pain occurred. The abdomen was soft. A month before admission the bowel movements were loose, and there had been increasing anorexia and a weight loss of 10 to 15 pounds. A few weeks before admission barium-enema study was negative except for marked dilatation of the cecum and the ascending and the transverse colon. The distention became more persistent, and during the week before admission frequent enemas were required for relief, although the bowel movements were spontaneous and normal. The patient vomited small amounts once or twice daily. Four days before admission a colonic irrigation gave considerable temporary relief.

Some years before the present illness an appendectomy had been followed by a phlebitis in the right leg. There had been attacks of mild cystitis, two and one year before admission, each lasting from a week to a day. Ten years before admission the pelvis had been fractured in an automobile accident.

Physical examination disclosed an obese patient who nevertheless showed signs of weight loss. The abdomen was distended, soft and nontender. Perianal skin was increased. No mass was felt. There were external hemorrhoids. Rectal examination was negative.

The temperature was 98.2°F, the pulse 88, and the respirations 20. The blood pressure was 140 systolic, 80 diastolic.

Examination of the blood revealed a hemoglobin of 14.2 gm and a white-cell count of 9700, with 32 per cent neutrophils. The urine was normal. No ova, parasites or red cells were found in the stools on repeated examination. The stools were guaiac negative. A barium enema revealed an area of rather marked narrowing in the middle and upper sigmoid over a distance of approximately 12 cm. The lumen was irregular, and in the mid-portion there was an uneven area that could have represented a pocket extending beyond the bowel lumen. There were a few diverticula in the distal sigmoid, but none in the region of the narrowing. The margins of the latter were not shelved. Barium passed beyond the obstruction showed considerable fecal material in the dilated colon. The small bowel was also dilated. Fluoroscopically there was thought to be a shadow behind the heart, possibly a hernia, but this did not contain colon.

On the second hospital day, proctoscopic examination was negative up to 15 cm above the anus. The patient's condition continued unchanged for nine days, when a cecostomy and a prophylactic bilateral femoral-vein ligation were performed. The postoperative course was satisfactory. The

colon was drained by a Miller-Abbott tube inserted through the cecostomy. The small-bowel distention gradually decreased but did not disappear. The urinary output, which was low for two days, subsequently increased. The serum protein had dropped to 3.6 gm per 100 cc by the fifth postoperative day. The white-cell count reached a maximum of 16,000 on one occasion, a transfusion with 500 cc of blood was given at the time of operation, and again on the fifth postoperative day. On the twenty-third hospital day a second operation was performed.

DIFFERENTIAL DIAGNOSIS

DR FRANCIS D MOORE This woman in the seventh decade of life, after six years of vague abdominal rumbling, which presaged further trouble, developed abdominal symptoms in a gradual crescendo that reached a maximum at the time of admission, when the previous, rather vague and intermittent symptomatology yielded to symptoms of obstruction with anorexia and weight loss. The significant items of that six-year history are the duration and the finding, a year before admission, of diverticulosis with spasm in the sigmoid, justifying a diagnosis of diverticulitis. This bout of difficulty had evidently subsided spontaneously, only to recur on various occasions prior to admission, the most recent episode taking the form of an intensified version of the previous ones.

The past history does not cast a great deal of light on the present symptoms except that, since the appendix had been removed, we presumably need not worry about that as a source of the present trouble.

On physical examination, the patient was noted to be obese, which as I shall point out later is probably significant. Examination of the abdomen showed low-grade, large-bowel obstruction. The patient was not systemically ill and had little evidence on physical or laboratory examination of invasive infection. The negative guaiac test was of course of great interest and probably significant, although it would be nice to know whether multiple tests were carried out. The x-ray findings, needless to say, are of the greatest importance.

X-ray study revealed narrowing, with neighboring diverticulosis. We need not waste time on the well known fact that the diverticula involved in acute diverticulitis often do not show in the x-ray film, owing to the fact that they are filled with purulent material, to edema of the mucosa or to fecal material, or to a combination of the three. The significant facts are that the margins of the defect were not shelved and that some obstruction was produced. Dilatation of the small bowel simply indicates that the ileocecal valve was not competent. The negative proctoscopic examination is of little help one way or another, since the patient's lesion was well above 15 cm from the anus. The lack of

blood on proctoscopy, however, corroborates the negative guaiac test

The initial operation performed — namely, a cecostomy and prophylactic bilateral femoral-vein ligation — is of some interest from a technical point of view, because it might have been predicted that a transverse colostomy would be a more satisfactory initial procedure in this particular patient. I imagine that prophylactic bilateral femoral-vein ligation was carried out not only because of the patient's age and the disease but also because of the previous phlebitis. After this operation the colon was drained by a Miller-Abbott tube inserted through the cecostomy, an ingenious method of large-bowel lavage worked out by Dr. J. B. Millet.¹ Again, I should like to know what disease the surgeons thought they were dealing with because, even with Miller-Abbott lavage of the large bowel through a cecostomy, I should not consider the bowel adequately prepared for resection of an inflammatory process. After this operation the urinary output was low for two days but subsequently increased, suggesting that the physiologic disturbance incident to operation was greater than had been expected. At the end of that time the serum protein was 3.6 gm. per 100 cc., and one wonders if this was an accurate determination or if the patient had possibly been overhydrated in an attempt to restore the renal function. On the twenty-third hospital day, after a transfusion, a second and presumably definitive operation was performed.

The differential diagnosis lies between carcinoma of the sigmoid and diverticulitis. There are a few other extremely rare conditions to be considered, such as endometriosis, invasion of the large bowel by tumor of a neighboring viscus and some of the rarer bowel tumors.

Because of the fact that the patient had had symptoms for six years, as well as a known diverticulosis and typical diverticulitis with spasm a year previously, and because of the negative guaiac test and the fact that no shelf was visible in the x-ray film, I take the point of view that the patient had diverticulitis, with spasm and obstruction, and a small area of localized perforation represented by the pocket of barium outside the lumen. She obviously had little systemic reaction to this perforation, which was probably chronic and caused no elevation of the white-cell count or temperature.

From time to time someone gets up enough curiosity concerning the subject of diverticulitis to look up a series of cases of this disease. Reviews by Smithwick,² in 1942, and Morton,³ in 1946, are examples of such clinical investigation. It might be worth while to review some of the figures in one of those articles and to determine whether our analysis of this case agrees with the figures in the article. According to Morton, diverticulosis is found in approximately 7 per cent of all post-mortem

examinations. This is merely another way of saying that one should not be too much influenced by the diverticula found in the x-ray picture.

In 200 cases of diverticulitis, 111 patients entered the hospital with diverticulitis and spasm, meaning that local narrowing in the sigmoid was an accompaniment of the systemic manifestations. The combination was noted in obese patients about four times as often as it was in thin patients and was equally distributed between men and women. Essentially all the patients were over forty years of age, and 94 per cent had pain as the outstanding symptom. About a third of these patients had distention, and it is of interest that in Morton's series 24 per cent gave a distinct history of having passed bloody stools and that in 32 per cent the benzidine test was positive for occult blood. This evidence shows that blood in the stools does not rule out diverticulitis, it is obviously important to mention, however, that with blood in the stools one must be suspicious of the diagnosis of diverticulitis and treat such patients with the presumption that carcinoma is present. In this particular case, however, since the guaiac test was negative and proctoscopic examination revealed no blood, the diagnosis inclines toward diverticulitis.

In Morton's series, 85 patients, or slightly less than 50 per cent, had various complications of diverticulitis. These complications were equally divided between perforation and obstruction, it is worthy of note, however, that perforation carried a 30 per cent mortality. It is also of the greatest importance to observe that 17 of these patients had carcinoma. The neoplasms were in the sigmoid in 12 cases and elsewhere in the colon in 5. This may be stated otherwise by pointing out that 10 per cent of patients who have diverticulitis with complications also have carcinoma of the colon. The significance of this consideration in evaluating this particular patient is obvious.

It is also worthy of note that 25 per cent of the obstructed patients also had a small abscess, which would apply to this patient, and that 50 per cent of the obstructed cases were completely obstructed. The patient in the case under discussion was not completely obstructed.

Thus, when we try to determine how this patient fits into the broad picture of diverticulitis, we see that in many ways she is quite typical of patients with the disease.

That brings us to the final point of the difference between the surgical diagnosis and the surgical strategy in handling a case. My diagnosis in this case is diverticulitis, with partial large-bowel obstruction and a small localized perforation producing an abscess.

In dealing with this patient, however, one must consider the lesion to be carcinoma until it is proved otherwise. By this I mean that, even when the

ologist has the specimen on the table, he may be able to tell whether or not a cancer is present, the operation carried out must be radical enough to satisfy the requirements of cancer surgery. In view of the fact that considerable inflammatory mass may be present, the bowel should be prepared in such a way that a safe resection can be made, if the lesion is diverticulitis — that is, by a transverse colostomy that comes as close to defunctioning the colon as is possible. It is my feeling in this particular case another, possibly less satisfactory, maneuver was carried out, although it is only fair to say that on admission the patient may have had such a dilated colon that a satisfactory transverse colostomy would have been difficult and dangerous of accomplishment. In any event, after a suitable period of defunctioning of the distal colon with an attempt to produce a surgically satisfactory and bacteriologically clean if not sterile bowel, an adequate radical resection of the area could be carried out with a diagnosis of diverticulitis or with a strong suspicion of carcinoma.

CLINICAL DIAGNOSES

Diverticulitis
Carcinoma of sigmoid

DR MOORE'S DIAGNOSIS

Diverticulitis, possibly with superimposed carcinoma

ANATOMICAL DIAGNOSIS

Diverticulitis, acute and chronic

PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY: The specimen received at the laboratory was a segment of sigmoid measuring 25 cm in length. The middle third was markedly thickened and narrowed and felt quite firm. Its serosa was covered with fibrin, the bowel wall was thickened to 6 mm, and the mucosa was thrown into pseudopolypoid folds. Numerous diverticula were present in both the constricted portion and the proximal sigmoid above it. As Dr Moore prophesied, it would have been impossible to exclude carcinoma on gross examination, but many microscopic sections showed only acute and chronic inflammation.

DR ARTHUR W. ALLEN: Dr Moore has summed up this situation admirably. There was no question about the diagnosis of diverticulitis in this case. We were, however, confronted with problems that were perhaps not made entirely clear in the record. One was that, in spite of all our efforts, this woman maintained a serum protein level of about half the normal. We believed that she was much too distended at the time she came in for a transverse

colostomy, which would have been the operation of choice. Also, she had dilated loops of small bowel, which might have indicated an incompetent ileocecal valve but were later proved to have been due to partial obstruction of the small intestine caused by adhesions to the inflammatory mass.

A cecostomy was done as a temporary measure. We had expected to do a transverse colostomy later after the decompression had partly subsided. Millet's method of deflating the colon with the Miller-Abbott tube was quite effective, but the patient still seemed to have dilated loops of small intestine. This caused us to attack the problem of relieving her of the secondary small-bowel obstruction. When the area was exposed, it was evident that she could not have improved had not the loop of small bowel attached to the inflammatory lesion been freed. This was easily accomplished, and it was not necessary to resect any small bowel. Instead of stopping at this point and hoping that the areas of small intestine would not become reobstructed, we elected to remove the disease in the sigmoid at the same time. A number of factors were involved in this decision.

We were dealing with a patient who, first of all, refused to have any surgery done. After five days, she agreed to let us proceed. When we told her that she would need three operative procedures before she was well, — namely, transverse colostomy, removal of the lesion at some later date and, finally, closure of the transverse colostomy, — she simply refused. A cecostomy was done, in the hope that possibly we might avoid a three-stage procedure and make it a two-stage operation.

At the second operation, after the small bowel had been freed, the sigmoid was carefully examined and felt not like diverticulitis alone but definitely like carcinoma. This influenced us somewhat in proceeding with a resection of the sigmoid at that time. We have seen carcinoma and diverticulitis associated in several cases and were swayed by this in removing this segment of the sigmoid. It proved, however, that diverticulitis with a phlegmonous mesentery of the bowel was the true situation and that no cancer was present.

DR MOORE: Dr Allen's comments have filled out the picture in a fashion that would be difficult to put in the case protocol. Excessive distention certainly made an initial transverse colostomy impossible, and the continuing small-bowel obstruction forced the issue before further colonic preparation could be carried out.

My comments about the methods of preparation of the bowel were intended merely to bring out the point that adequate preparation of the segment to be resected is of the greatest importance if one is dealing with diverticulitis alone. One or two near disasters that we have had on the surgical service in the last two years, which resulted from resection

with inadequately prepared bowel, merely point out the significance of these considerations in diverticulitis.

The real difficulty, however, from a practical point of view, is nicely demonstrated by this patient and therefore is possibly worth an additional word. The problem can be stated as follows: if one is dealing with carcinoma, a resection after a week or two of preparation even by cecostomy alone, with or without the Millet device, is perfectly satisfactory, and in dealing with diverticulitis a total defunctioning transverse colostomy, with a rest of several months, is ideal. Yet from Morton's figures and those of others we find that diverticulitis and carcinoma coexist so frequently that the surgeon is often taking on himself an inordinate risk by letting the patient with what is considered to be diverticulitis rest at home for four to six months before resection is done.

Because of this fundamental problem and the difficulty of ruling carcinoma in or out we are often forced to a sort of compromise that in the occasional

case of diverticulitis alone produces " " results. I recall well a patient in whom this differential choice existed and in whom I carried out a combined abdominoperineal resection with extensive pelvic dissection and, of course, a perineal colostomy, only to find that there was nothing but diverticulitis in the specimen.

I think that we should therefore give all the encouragement we can to those who are working on more adequate methods of diagnosing the presence of carcinoma.

DR MALLORY: The postoperative complications that were feared developed in this patient. Gangrene of the bowel occurred on either side of the suture lines, followed by perforation and general peritonitis. There was a terminal bronchopneumonia.

REFERENCES

1. Unpublished data.
2. Smithwick, R. H. Experiences with surgical management of diverticulitis of sigmoid. *Ann Surg* 115:969-985, 1942.
3. Morton, J. J., Jr. Diverticulitis of colon. *Ann Surg* 124:715-745, 1947.

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

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icine 8 Fenway Boston 15 Massachusetts

OLIC ACID

THE term "folic acid," originally used for a substance in spinach required for the growth of *Streptococcus lactis* R, is now applied to a group of substances found in yeast, liver, green leaves, cereals and other foods that are considered to be members of the vitamin B complex. The group includes vitamin B₁₂, required for the prevention of nutritional anemia in chicks, vitamin M, necessary for the prevention of nutritional cytopenia and a sprue-like syndrome in monkeys, and factors needed to prevent nutritional anemia in rats treated with sulfonamides to inhibit vitamin synthesis by intestinal bacteria. Also included are factors promoting the growth of *Lactobacillus casei* and *Str. lactis* R. The *L. casei* factor, also effective in the treatment of the animal nutritional deficiency syndromes men-

tioned above, has been isolated from liver and synthesized. It is a compound of a pteridine, related to the yellow color in butterfly wings, para-amino benzoic acid, a well known antagonist of sulfonamides, and glutamic acid, an amino acid, and has been named pteroylglutamic acid. Conjugates of this substance with two or six additional glutamic acid groups have also been isolated.

The interest to the medical profession in this group of substances lies in the ability of some of them to produce remissions in several nutritional macrocytic anemias, including pernicious anemia, and especially in the relation between pteroylglutamic acid and its conjugates and the principle in liver effective in Addisonian pernicious anemia.

The amount of solids in purified liver extracts is far less than the amount of folic acid required to give comparable hematologic effects, and the folic acid content of such liver extracts is negligible. In contrast to liver extract, folic acid is equally effective orally and by injection. It is thus clear that folic acid is not the principle in liver extract effective in pernicious anemia, nor is it the extrinsic (food) factor or the intrinsic (gastric) factor described by Castle. Folic acid does not restore the secretory activity of the stomach in pernicious anemia, at least so far as hydrochloric acid is concerned.

Liver principle is thought to produce folic acid, possibly by aiding enzymes known as conjugates in releasing free folic acid from the conjugated forms in which it appears in foods.¹ Folic acid, in turn, may act as an enzyme in the production of 5-methyluracil (thymine), a component of nucleic acid, which is also effective in pernicious anemia and related states but only in doses over a thousand times as great as that of folic acid.²

Nutritional macrocytic anemias that respond to injections of purified liver extract are thought to arise because of deficient intake of extrinsic factor, defective secretion of intrinsic factor or defective absorption of these substances or products of their interaction. Combinations of these mechanisms frequently exist. As was first shown by Spies and his associates,³ folic acid acts approximately as well on the blood and bone marrow in these cases as purified liver extract. This group of anemias includes Addisonian pernicious anemia, megaloblastic anemia of

infancy and some cases of nutritional macrocytic anemia occurring with poor diets alone or in association with sprue, pellagra, chronic alcoholism, carcinoma of the stomach or pregnancy. In sprue it has been claimed that the stools improve and that the intestinal motility, atrophied mucous membranes and glucose-tolerance tests return to normal.

Purified liver extracts in the usual doses effective in Addisonian pernicious anemia do not relieve the anemia due to a deficiency of Wills's factor.⁴ The anemia can, however, be corrected promptly by crude liver preparations. Such cases have been noted in association with defective diets, either alone or accompanying pregnancy or steatorrhea. Only three such cases have been treated with folic acid.⁵ The response was partial, and further improvement followed crude-liver therapy.

The effective dose of folic acid is 5 to 20 mg daily by mouth or by injection, 10 mg daily being sufficient in most cases to produce remissions comparable to those obtained with purified liver extracts. Daily dosage seems advisable, since patients treated in this way may show maintenance of normal blood counts, whereas results are less satisfactory if folic acid is given in large doses every one or two weeks. This is not surprising in view of the fact that one third to one half of a 10-mg dose of folic acid may be lost in the urine within twenty-four hours. No toxic effects have been noted with single doses as large as 400 mg.

Folic acid as a practical therapeutic agent does not, however, directly provide "new hope for anemics." Thus, there is no anemia that folic acid relieves that is not also relieved by liver extract. Crude liver extracts have produced complete remissions in cases due to a deficiency of Wills's factor after failure of folic acid to do so. Liver extracts are effective in the prevention and arrest of combined system disease, whereas there is growing evidence that neurologic disturbances in pernicious anemia may remain unaltered or even progress, sometimes in a rapid and dramatic fashion, under folic acid therapy, even when the red-cell count is maintained at a normal level.⁶

Two features of folic acid have been claimed as therapeutically useful. In the first place, it is suggested that oral therapy would remove the necessity

for repeated injections. This, however, appears to be a disadvantage in pernicious anemia, since neglect of therapy occurs too frequently when patients treat themselves with oral medicines. In any case the possibility of neurologic complications outweighs any advantage that the oral route of treatment may have. Good health is usually maintained in pernicious anemia with an injection of 1 or 2 cc of purified liver extract as seldom as every two or four weeks. Secondly, folic acid has been recommended for cases allergic to liver extracts. Dr. C. S. Davidson,⁷ however, has recently shown that in a series of fourteen cases sensitive to pork-liver extract given parenterally all cases reacted favorably to beef-liver extract in spite of skin tests in some cases showing apparent sensitivity to the latter. These findings, together with the arguments mentioned above, make the use of folic acid in these cases unnecessary and undesirable.

Like liver extract, folic acid has failed to produce remissions in refractory and aplastic anemias, leukemias, myelophthisic anemias and megaloblastic deficiency anemias, as well as in neutropenias occurring spontaneously or those due to sulfonamides, thiouracil or influenza. The possible beneficial effect of folic acid on the neutropenias due to exposure to radium and x-rays should be readily subject to analysis by animal experiment.

REFERENCES

1. Welch, A. D., Henle, R. W., Nelson, E. M., and Nelson, H. V. Effective utilization of conjugated pteroylglutamic (leucovorin) in pernicious anemia. *J. Biol. Chem.* 164:787, 1946.
2. Frommeyer, W. B., Jr., Spies, T. D., Vilter, C. F., and English, J. Further observations on anti-anemic properties of 5-methyltetrahydrofolic acid. *J. Lab. & Clin. Med.* 31:643-649, 1946.
3. Spies, T. D., Vilter, C. F., Koch, M. B., and Caldwell, M. H. Observations of anti-anemic properties of synthetic folic acid. *St. M. J.* 38:707-709, 1945.
4. Watson, J., and Castle, W. B. Nutritional macrocytic anemia, especially in pregnancy: response to substance in liver other than folic acid effective in pernicious anemia. *Am. J. M. Sc.* 211:513-530, 1946.
5. Davidson, L. S. P., and Girdwood, R. H. Folic acid in treatment of megaloblastic anaemia. *Lancet* 2:373-376, 1946.
6. *Veterans Administration Technical Bulletin*, December 10, 1946.
7. Davidson, C. S. Personal communication.

TIME OUT

EVEN physicians need vacations whether they know it or not. One grows older insensibly, our confreres recognize this aging in us while we ourselves frequently do not. So likewise our professional duties pall, be it ever so gradually, our patients' little aches and pains, so real to them, irritate and we are prone to brush them aside as irrelevant.

important. We lose interest in our work and, perhaps, become irritable to others, and that very irritability galls us and makes us still more irritable. Headaches and pains of no great moment. Our doctor tells us that they are due to this or organic defect — which, incidentally, we have for the past ten years. This train of events increases in geometric proportion until something happens, and even we ourselves recognize that we must leave the traces and be off, come hell or high water.

There are some physicians who, in actuality, do need a vacation in the true sense of the word. The fortunate persons can keep themselves in fine fettle both mentally and physically by taking a long weekend in the country now and then as the spirit moves them. They are to be envied. There are others who “knit up the unravelled sleeve of care” by throwing themselves into the noisome turmoil of a large city. The great Nissl is said to have taken his time off by packing a small suitcase half of cigars, covering them with a piece of cardboard and filling the remaining space with cigars. He traveled by train — to nowhere in particular — until the intervening cardboard was reached. Then retraced his steps. In other words, there are all sorts of vacations.

Where does the physician's physician fit into this picture? As a rule his problems are three. Is there something really wrong? What is it? What should be done about it? Not infrequently the first question is the most difficult of all. There is both conscious and unconscious malingering. There is both conscious and unconscious rationalization of one's signs and symptoms. There is the unconscious tendency of the physician-patient to put two and two together and make five, just as there is, at times, a cheerful effort to put five and five together and garner one. The physician is notoriously a difficult patient. At knowledge he has, be it great or small, is liable to become distorted. He usually cannot evaluate his symptoms in an objective and dispassionate manner. Indeed, it is the rare physician who can sit back and simply and without emotion “Behold, I have a symptom. What shall I do about it?”

If this editorial seems to wander from the subject, it is because physicians, unless confronted by a concrete problem, are prone to do just that. The thesis

is simply this: some men are ill and need meticulous care and protection, whereas others with symptoms no less severe are simply worn out mentally and physically and in grievous need of a vacation. It is then the attending physician's problem to size the situation up — to be sure that there is nothing really wrong — to take such measures as are necessary to prove that this is the case and then to insist that his patient take a vacation, one to his own liking and, above all, *enrêlé*. To place a sharp limit on the duration of a tired man's vacation automatically nullifies its beneficial effect.

It takes a brave and sagacious man to say to a fellow physician with marked symptoms “Do you really want to take that trip? Then do.”

MISCELLANY

NOTES

The appointment of three new professors at the Harvard Medical School has been recently announced. Dr Robert E. Gross has been made William E. Ladd Professor of Child Surgery and head of the Department of Surgery at the Children's Hospital. Dr William T. Green becomes clinical professor of orthopedic surgery and director of orthopedic surgery at the Children's Hospital. Dr Joseph S. Barr becomes clinical professor of orthopedic surgery and director of orthopedic surgery at the Massachusetts General Hospital.

The following Massachusetts physicians were recently appointed fellows in the American College of Surgeons: Ronald W. Adams, Boston; Felicia A. Banas, Boston; James B. Blodgett, Boston; Francis M. Burke, Nauck; Bradford Cannon, Boston; George D. Dalton, Quincy; Lawrence R. Dame, Greenfield; John F. Flynn, Pittsfield; George R. Gagliardi, Framingham; Ilija Galleani, Boston; Francis M. Ingersoll, Boston; Aurel G. Lavoie, Springfield; Samuel Levine, Lynn; Saul M. Marcus, Boston; Carroll C. Miller, Boston; Daniel L. Moonen, Fall River; Francis D. Moore, Brookline; Daniel J. Mullane, Brookline; Philip E. Mullane, Lowell; John A. Reidy, Boston; Arnold L. Segel, Boston; Clarke Staples, Malden; Joseph M. Stowell, Boston; and Charles L. Sullivan, Brookline.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Radio in Health Education. Prepared under the auspices of the New York Academy of Medicine. 8°, cloth 120 pp. New York: Columbia University Press, 1935. \$1.60.

This monograph is the first in a new series, entitled *Frontiers in Public Health Education*, and is intended for the use of health educators, social workers, radio personnel, health organizations and all others concerned with public health. The first part of the text is a critical analysis of radio broadcasting made under the auspices of the New York Academy of Medicine. The second part consists of papers presented at a public-health conference held in December, 1943, at which the various aspects of the radio program were discussed. An appendix gives a response analysis of a series of talks, entitled “Highways to Health,” given over the air during the period from June 9, 1935, to November, 1939. A total of two hundred and twelve auditions were given on twenty-six different subjects. The number of talks on each

subject varied from thirty-nine on the problems in the care of children to two on varicose veins, goiter and other subjects. The average response was one hundred and ninety-four, and two tables show the responses higher and lower than the average. The highest response (nine hundred and twenty) was to a talk on the skin troubles of the young, and the lowest (two) was on the care of the skin in summer. It is interesting that the second highest response (nine hundred) was on arthritis. The radio is an instrumentality of communication with enormous potentialities, and the material presented in this monograph comprises a basic and critical evaluation of objectives and technics in radio health education. This monograph should be in all medical libraries and should prove valuable to all persons interested in public health.

The Diagnosis of Nervous Diseases. By Sir James Purves-Stewart, KCMG, CB, Knight of St John of Jerusalem, M.D. (Edin.), FRCP, consulting physician to Westminster Hospital, West End Hospital for Nervous Diseases and Royal National Orthopaedic Hospital. Ninth edition. 8°, cloth, 880 pp., with 358 illustrations. Baltimore: The Williams and Wilkins Company, 1945. \$11.00.

This standard work, whose first edition was published in 1906, has been consistently revised throughout all its editions. The work has been rewritten so far as possible amid the strains of World War II. The author, while traveling from the United States to England in 1943, lost all his manuscripts and notes by enemy action and therefore had practically to rewrite the whole book on the basis of previous editions and material available in London.

Pediatric X-Ray Diagnosis: A textbook for students and practitioners of pediatrics, surgery and radiology. By John Caffey, M.D., associate professor of pediatrics, College of Physicians and Surgeons, Columbia University, associate pediatrician and roentgenologist, Babies Hospital and Vanderbilt Clinic, New York City, and consulting pediatrician, Grasslands Hospital, Westchester County, New York, and St John's Hospital, Yonkers, New York. 4°, cloth, 838 pp., with 710 illustrations. Chicago: The Year Book Publishers, Incorporated, 1945. \$12.50.

This is the first complete book on roentgenologic diagnosis in pediatrics published in English since that of Thomas Morgan Rotch, of Boston, on the diagnosis of diseases in early life by the roentgen method, issued in 1910. The author has based his work on the roentgenologic conferences held semimonthly at the Babies Hospital, New York City, during the last twenty years. The purpose of the work is to describe the shadows cast by normal and morbid tissues and the clinical appraisal of roentgenologic findings in pediatric diagnosis. Physics, technic and therapy have been omitted intentionally. To each topic is appended a short list of references to the literature. The book is well printed, with a good type, on coated paper. The illustrations are clear, and the roentgenograms clearly defined. This book should prove valuable in all medical-reference collections.

Surgical Treatment of the Motor-Skeletal System. Supervising editor Frederic W. Bancroft, M.D., associate clinical professor of surgery, Columbia University, attending surgeon, New York City and Beth David hospitals, consulting surgeon, Veterans Administration, Lincoln and Harlem hospitals, New York, and Kings Park State Hospital, Kings Park, New York. Associate editor Clay R. Murray, M.D., professor of orthopedic surgery, College of Physicians and Surgeons, Columbia University, attending surgeon and chief of the Fracture Service, Presbyterian Hospital and Vanderbilt Clinic, New York City, consulting surgeon, Hackensack General Hospital, Hackensack, New Jersey, Sharon Hospital, Sharon, Connecticut, and St. Joseph's Hospital, Far Rockaway, New York. Part One: *Deformities, Paralytic Disorders, Muscles, Tendons, Bursae, New Growths, Bones, Joints, Amputations*. 4°, cloth, 641 pp., with 520 illustrations and a color plate. Part Two: *Fractures, Dislocations, Sprains, Muscle and Tendon Injuries, Birth Injuries, Military Surgery*. 4°, cloth, 639 pp., with 543 illustrations. Philadelphia: J. B. Lippincott Company, 1945. \$20.00.

This new treatise, a composite work of forty-three authorities in their particular fields, is primarily on surgical treatment, and therefore no attempt has been made to present the diagnostic problems or the etiology of the conditions in general. Selected lists of references are appended to each chapter. The text is well printed, with a good type, on paper, but because of the necessity of using coated paper for the illustrations, the volumes are rather heavy for their size.

A Handbook on Diseases of Children including diseases of the common fevers. By Bruce Williamson, M.D. (Edin.), FRCP (Lond.), physician, Royal Northern and Prince of Wales hospitals, London, and physician (E.M.S.), Wellbarn Hospital, Barnet. Fourth edition. 12°, cloth, 388 pp., with 81 illustrations. Baltimore: The Williams and Wilkins Company, 1945. \$4.50.

This fourth edition of a popular manual designed for medical students has been thoroughly revised, and recent advances in pediatrics have been introduced throughout the text. The colored plates, first introduced in the third edition, have been retained in this edition.

The Science and Art of Medicine: An inaugural lecture. By Sir Lionel Whitby, CVO, MC, MD (Cantab.), FRCP (Lond.), DPH, Regius Professor of Physics, University of Cambridge. 12°, paper, 24 pp. New York: Cambridge University Press, The Macmillan Company, 1946. 50 cents.

In this inaugural address on assuming the office of Regius Professor of Physics, Cambridge University, Dr. Whitby briefly outlines the work of his predecessors, and selects for a brief exposition one aspect of scientific medicine, that of chemotherapy.

Pharmacology. By J. H. Gaddum, Sc.D., MRCS, LRCP, professor of pharmacology, University of Edinburgh. Oxford: Medical Publications. Second edition. 8°, cloth, 460 pp., with 75 illustrations and 17 tables. New York: Oxford University Press, 1945. \$6.00.

This second edition of a textbook written primarily for medical students has been brought up to date and improved in other ways. A limited number of references have been incorporated throughout the text. An appendix on the interpretation of chemical names should be found helpful. The material is well organized and well printed on a good paper with a large type and the manual should prove valuable as a short text on its subject.

NOTICES

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 13

FRIDAY, FEBRUARY 14

*9:00-10:00 a.m. Clinicopathological Conference. Drs. Chester S. Keefer and H. E. MacMahon. Joseph H. Pratt Diagnostic Hospital.

*10:00 a.m.-12:00 p.m. Medical Staff Rounds. Peter Bent Brigham Hospital.

12:00 p.m.-1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

MONDAY, FEBRUARY 17

*12:15-1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, FEBRUARY 18

12:00 p.m.-1:00 p.m. Dermatological Service. Grand Rounds. Amphitheater. Dowling Building, Boston City Hospital.

*12:15-1:15 p.m. Clinicoradiological Conference. Peter Bent Brigham Hospital.

WEDNESDAY, FEBRUARY 19

*9:00-10:00 a.m. Pediatric Clinicopathological Conference. Drs. James M. Barry and H. E. MacMahon. Joseph H. Pratt Diagnostic Hospital.

*11:00 a.m.-12:00 p.m. Medical Clinic. Amphitheater. Children's Hospital.

(Notices continued on page xix)

The New England Journal of Medicine

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Volume 236

FEBRUARY 13, 1947

Number 7

REHABILITATION OF PATIENTS TOTALLY PARALYZED BELOW THE WAIST, WITH SPECIAL REFERENCE TO MAKING THEM AMBULATORY AND CAPABLE OF EARNING THEIR LIVING*

III. Tidal Drainage, Cystometry and Bladder Training

DONALD MUNRO, M D †

BOSTON

TIDAL drainage, cystometry and bladder training are interdependent. When properly used in combination they ensure that every patient who has had an injury to the spinal cord, conus or cauda equina and who is intelligent and co-operative will have infallible twenty-four-hour control of urination regardless of the severity of the cord injury. This paper is devoted to a description of the necessary apparatus and a discussion of the technic of these three therapeutic aids in such cases.

TIDAL DRAINAGE

Tidal drainage is a method whereby the urinary bladder can be alternately and automatically filled and emptied, the intravesical pressure constantly maintained at a predetermined level, puddling of residual urine and overstretching or shrinkage of the bladder wall prevented and the bladder maintained in a close approximation to a physiologically normal state even when completely separated from the suprasegmental part of the central nervous system. Although the apparatus, which was first described in 1935,¹ has subsequently been modified and improved, the principle of operation remains the same. Its proper use depends primarily on cystometrographic demonstration of the type of bladder that is to be served. Those hydrodynamic laws that have to do with siphonage determine its activity. Its proper functioning depends on the maintenance of an airtight siphon system during the period of emptying of the bladder.

Siphonage is activated whenever a predetermined intravesical pressure has been reached. The siphon is broken and inactivated by the admission of air as soon as the bladder is emptied. The apparatus is thereby left in such a condition that the cycle can start over again. The control of the admission of air into the system was accomplished in the

original apparatus by the use of a water trap. This trap had to be filled before the bladder was filled and before the siphon system could be made airtight, it had to be emptied after the bladder had been emptied before the siphon could be broken. Subsequent improvements led the irrigating fluid directly to the bladder² rather than by way of the trap (Fig. 1) and then replaced the trap with a capillary tube.³ The bore of this tube is too small to permit enough air to enter to break the siphon so long as the system contains any fluid. Through the ingenious use of a four-outlet Carrel-Dakin glass connector, a built-in cystometer is included along with this air vent (Fig. 2). Finally, the air vent and cystometer have been amalgamated⁴ by the use of a tube with a large enough bore to act as a cystometer, the apparatus is given the features of the air vent by being made airtight except for the air that enters and escapes through a hypodermic needle thrust through a rubber connection at its top (Fig. 3). All previous models have been abandoned in favor of these last two, which have been given extensive and thorough trials in my clinic. Both are entirely and equally satisfactory if properly constructed, set up and used. Neither is adequate unless used in conjunction with cystometrograms made once a week, or oftener if the occasion requires it.

Construction of the Tidal-Drainage Apparatus

As will be seen from Figures 2 and 3, there are certain parts of the apparatus that are common to both models. These are the following:

A wooden stand, equipped for attachment to the foot or head of the bed, measuring $6\frac{1}{2}$ feet long by 4 inches wide and with a shelf 6 by 6 by 1 inches at either end and on opposite sides. A centimeter scale marked every 0.5 cm. with its zero at the same level as the patient's pubis, is applied to the side of the upright that the lower shelf is on, the zero indicating the bladder level referred to in the figures and the text below.

A 2500-cc. aspirator bottle to which an airtight Murphy dropper that does not have a hole in its side is attached by

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an appropriate length of rubber tubing, an adjustable compression clamp controlling the rate of flow through the dropper. The aspirator bottle is strapped in place on the top shelf of the stand and the inlet is closed with a sterile gauze or cotton plug.

A waste bottle corked with a doubly perforated stopper containing short pieces of glass tubing in the perforations.

A No 16 Fr soft-rubber rectal tube for use as a catheter in male patients, and either that or a No 16 Fr soft-rubber

connector is 5 cm below the bladder level and so that the cystometer tube lies beside the centimeter scale that is on the wooden upright.

A Y tube. The aspirator bottle and attached airtight Murphy dropper are connected by a sufficiently long piece of rubber tubing to one arm of the Y tube, whose upright is inserted in the open end of the catheter. Another equally long piece of rubber tubing is led from the other arm of the Y to the open end of the Carrel-Dakin connector.

A length of small (inside diameter, 3 to 5 mm) rubber tubing, attached to the third side opening of the Carrel-Dakin connector. This tubing is carried upward to some point higher than the bladder level, passed through a loop of siphon (this makes the siphon curve) and then led downwards, attached to one of the glass tubes in the cork in the waste bottle. The other glass tube remains open. The waste bottle stands on the lower shelf of the wooden upright.

To construct the apparatus shown in Figure 1, the following material is needed in addition to the basic equipment listed above:

A piece of glass tubing 70 cm long and with a bore of about 3 mm (the cystometer tube), whose upper end is at

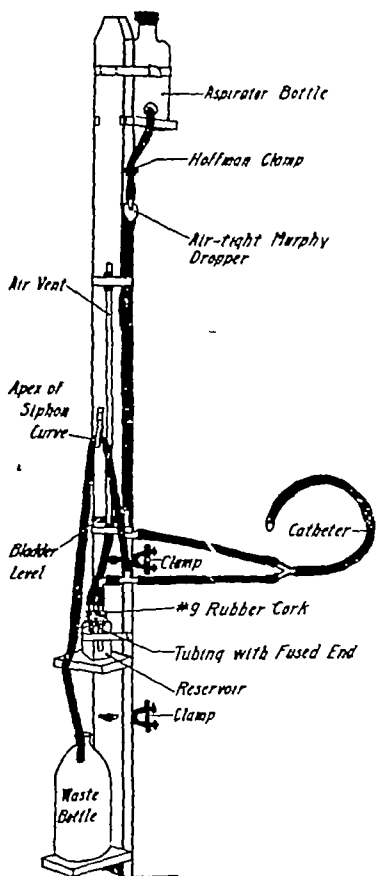


FIGURE 1 Original Tidal-Drainage Apparatus as Modified by MacNeill and Bowler²

mushroom catheter for use in female patients, held in place by appropriate adhesive strapping applied to the penis or the pubis respectively. It is important that the maximum size of the catheters be limited to No 16³.

The irrigating fluid used in both models is either Solution M or Solution G⁶. It is sterilized by autoclaving in the usual manner.

To construct the apparatus shown in Figure 2, the following additional material is needed:

A four-outlet (three lateral and one terminal) Carrel-Dakin glass connector.

A glass capillary tube 70 cm long. This is the air vent and is attached by rubber tubing to the center of the three side openings of the Carrel-Dakin glass connector.

A piece of glass tubing 70 cm long with an inside bore of about 3 mm. This is the cystometer tube and is attached to the lateral opening that is closest to the closed end of the Carrel-Dakin glass connector by a piece of rubber tubing surrounded by a compression clamp, which is closed when the apparatus is used for tidal drainage and opened when it is used as a cystometer. The Carrel-Dakin connector, with the air vent and cystometer tube attached, is strapped to the wooden upright in such a position that the horizontal center line of the

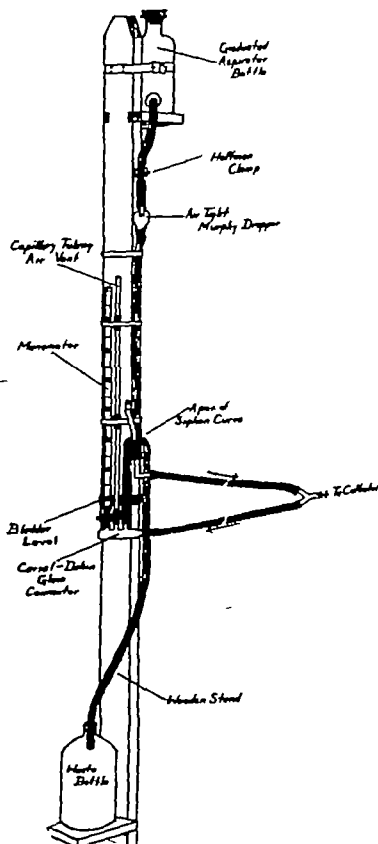


FIGURE 2 Tidal-Drainage Apparatus as Devised by Stewart. The trap is replaced by a capillary tube, and there is a built-in cystometer.

attached by a short piece of rubber tubing to the outlet of the airtight Murphy dropper.

A hypodermic needle with a patent bore, which is thrust through one wall of the rubber tube. This is the air vent.

A Y tube, one of whose arms is joined by rubber tubing to the lower end of the cystometer tube, the upright being connected to the open end of the catheter with the help of rubber tubing and glass connectors. The cystometer is

he attached Y tube are then strapped to the wooden in such a way as to place the former beside the center scale with its lower end 5 cm below the bladder

length of small rubber tubing (inside diameter 3 to 5 mm), which is led upward from the other arm of the Y tube to a point higher than the bladder level, passed through a piece of adhesive (this makes the siphon curve) and then led downward to be attached to one of the glass tubes in the cork of the waste bottle, the other glass tube remaining open. The waste bottle is placed on the lower shelf of the wooden stand

In this apparatus the 70-cm glass tubing serves not only as part of the irrigating system but also as the graduated arm of a cystometer and, by virtue of the hypodermic needle, as an air vent

The catheter should be removed, cleaned, re-sterilized and replaced — if again needed — once a week. Both types of apparatus should be taken down, cleaned and re-sterilized once a week while in use

It has been the custom in my clinic to attach the apparatus to the foot of the bed, but they work equally well when attached to the head or when mounted on an operating upright

Causes of Functional Failure

No matter which model is used certain simple precautions must be observed in its operation otherwise the apparatus will fail to work. This usually happens because the siphon is broken prematurely. As a result, the bladder either is not permitted to fill sufficiently to raise the intravesical pressure level to the desired height or is not completely emptied at each cycle

Air leaks, which are the most frequent cause of trouble, generally develop because of either or both of two mistakes. The usual one is to attempt to use a Murphy dropper with a hole in its side instead of the recommended type. Such a hole is excessive when used with either model and especially so with the combined cystometer-tube air vent (Fig 3), where it is too large to act as a substitute for the hypodermic needle. As a result, too much air enters the system. Even if it is closed with a piece of adhesive tape or bone wax, or both, and whether or not a hypodermic needle is stuck through the adhesive plaster, air leaks through because the suction effect during emptying is strong enough to pull air through the tape and to loosen the wax. The other mistake is to use rubber tubing that has too large an inside diameter for the siphon itself. This applies to both models. During emptying in such a case, the column of liquid flows only down the wall of the tube. Air is thus permitted to rush in through the unsealed center. A tube that is small enough to make the fluid column solid prevents this. In the model illustrated in Figure 2, an air leak may also develop if the clamp at the base of the cystometer tube is not tightly shut

Another cause of trouble is the formation of a trap in the long catheter connections. This occurs when the tubes are permitted to hang in a loop below the

level of the mattress. These rubber tubes should be pinned to the bedclothes on top of the mattress

Kinks in the connections, clamps that have been put on to stop the flow temporarily and then have not been removed, improperly placed catheters and hypodermic needles occluded by rust are further sources of trouble

Leakage of urine around the catheter occurs only because the apparatus has not been properly ad-

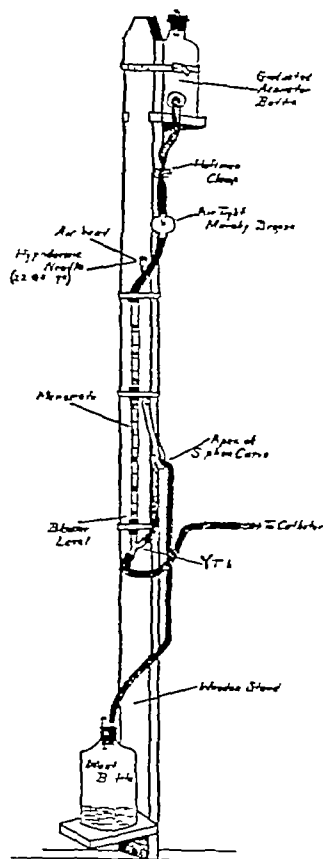


FIGURE 3 Stewart's Modification of the Tidal-Drainage Apparatus as Modified by Cone and Bridgers⁴
A hypodermic needle is substituted for the capillary tube

justed to the type of bladder it is serving. The remedy is to readjust the tidal-drainage apparatus after a cystometrogram has provided the necessary information regarding the stage of bladder recovery. The one thing not to do for this difficulty is to increase the size of the catheter — this will not stop the leak and will cause urethritis, epididymitis, prostatitis and the like⁵

Adjustment of Height of Siphon Curve

The proper height of the siphon curve varies with the stage the bladder has reached in its recovery. As pointed out in greater detail below, bladders

associated with significant injuries of the spinal cord or cauda equina pass through four such stages. These are recognizable only by cystometry and vary unpredictably in duration.

Immediately after injury the bladder is atonic. For this stage the siphon curve should be set at 1 or 2 cm above the bladder level. Recovery progresses through the stages of autonomicity and hypertonicity to the reflex or automatic phase. The siphon curve should be set at 2 to 5 cm above the bladder level for the autonomous, at 15 to 18 cm for the hypertonic and at 10 to 12 cm for the reflex bladder. If the occasion arises—for example, in a patient who is completely unconscious following a severe head injury—when tidal drainage must be used in connection with a normal bladder the siphon curve should be set at 10 to 12 cm above the bladder level, as in the reflex or automatic bladder.

CYSTOMETRY

By cystometry it is possible to determine what the functional activity of the bladder is at the time the cystometrogram is made. As a method of examination it does not pretend to be and cannot be more than relatively exact. If the cystometer and the method of using it approximate as closely as possible the normal physiologic process of filling the human bladder, however, this relative exactitude is sufficient for the purpose at hand. I believe this requirement to be of considerable importance particularly in view of the fact that a number of authors⁷⁻¹⁰ have advocated cystometric methods that do violence to this concept.

A normal bladder that is normally innervated receives urine from the ureters constantly and in small increments.¹¹ The increments are of the order of magnitude of drops. They never, under any circumstances, reach individual amounts of, for example, 10 cc at a time. An increment of 25 or 50 cc is physiologically fantastic. The bladder wall, certainly in human beings and probably also in such animals as the dog and cat, reacts in a physiologically normal manner to any normal increase in content. The musculature can and will react also to the admission at one time of larger amounts of fluid but not in the physiologic manner. Inferences regarding the normal activity of the bladder as the result of such abnormal stimuli are not justified and cannot be accepted as evidence for or against any conclusions other than that a purely experimental procedure that has no physiologic basis produces a certain type of muscular reaction. Conclusions based on such cystometric methods—as advocated by Rose,⁷ Voris and Landes,⁸ Langworthy and Hesser⁹ and Langworthy, Kolb and Lewis¹⁰—cannot therefore be accepted as explanations of normal bladder physiology. All the authors cited advocate cystometric methods in which unit increments of 25 or 50 cc of fluid are repeatedly introduced into the bladder.

The lethal effect of sepsis on the recovery of skeletal neuromuscular activity that has been previously altered by damage to the central nervous system is well recognized. The neuromuscular mechanism of the bladder can be shown to respond in the same way to this same complication.^{12,13} The deleterious influence of hypoproteinemia on the healing of bedsores, with resultant acute and chronic sepsis, was called attention to in 1940.¹⁴ Many writers have since confirmed this statement, and it is generally acknowledged that proper nutrition is essential for the cure of infection, as well as for the recovery of function and the well-being of patients with cord injuries. Experience with such patients in the Army¹⁵ and elsewhere merely emphasizes this fact. Many of Head's¹⁶ cases in which conclusions were drawn concerning bladder activity were palpably the result of chronic sepsis and probably also of hypoproteinemia. These data can no longer be ignored, and neurophysiologists, such as Fulton,¹⁷ should revise accordingly their concepts of bladder function in man. Interpretation of cystometric evidence without a knowledge of these and other variables is also impossible, and conclusions drawn therefrom are therefore untenable.

Technic

The observations reported herewith have been made with a cystometer that is to all intents and purposes a U tube¹⁸ (Figs 2 and 3) connected with the contents of the bladder by an unbroken column of fluid. Both ends of the U are open. When a cystometrogram is being made, a standard fill of 400 cc is used. This fluid is introduced into the bladder at a steady rate of not more than 90 drops a minute. Experiments have demonstrated that this is slow enough to reproduce the physiologic response to the normal filling that takes place by way of the ureters. In every case a catheter that is not of the Foley type is fastened in place in the bladder. The aspirator bottle in either type of tidal-drainage apparatus is replaced by a cylindrical glass container graduated in 25-cc amounts. The siphon curve is raised to 50 cm above the bladder level. The cystometer is first filled with an appropriate bland fluid, and all air bubbles are evacuated, after which it is closed off at the point of attachment to the catheter by a clamp. The bladder is then emptied, the catheter is attached to the cystometer, and the clamp is loosened. The compression clamp between the cylindrical container and the airtight Murphy dropper having been opened so that fluid flows at the proper rate of 90 drops a minute and the meniscus in the cystometer tube having been adjusted to the bladder level by the addition of any necessary fluids, it is possible to fill the bladder and read the intravesical pressure simultaneously. The pressure is read in connection with the height above zero of the meniscus in the cystometer tube. The amount of fluid that is in the bladder at any one

is determined by reading the fluid level in the cylinder. Changes in this level of as little as 1 cc. can be approximated with sufficient accuracy to justify recording. Each change in intravesical pressure—whether up or down—that is noted on the cystometer is recorded and opposite placed the amount of fluid that has run over into the bladder up to that point. An additional notation is made whenever there is leakage about the catheter whenever the cystometer tube or siphon curve flows. Recordings are continued until 400 cc of fluid has been run through the apparatus, unless there is reason to fear reflux up the ureters, in which case smaller amounts and lower pressures are used. The catheter is then disconnected from the apparatus and the bladder is allowed to empty itself with the open end of the catheter held at zero level. This urine is collected and measured. When this process is completed the catheter is lowered and any residual urine that flows out by siphonage is also collected and measured. The operator will then have two parallel columns of figures (one being intravesical pressure readings and the other intravesical cubic centimeters of fluid), as well as the amounts of the residual urine and the urine in the bladder at the close of the procedure.

Interpretation

From these data necessary information regarding bladder function can be obtained. The presence of emptying contractions is indicated when the intravesical pressure reaches or exceeds 50 cm of water, when there is leakage around the catheter or when either the cystometer or the siphon curve overflows. By noting the amount of fluid that has been delivered to the bladder between each succeeding emptying contraction, it is possible to determine the periodicity and frequency with which the contractions occur.

The curve of basic tonus can also be observed. By subtracting the lowest intravesical pressure from the highest and noting the amount of fluid that has gone through the apparatus, a fairly accurate estimate of the shape of the curve of basic tonus can be obtained. This is a function of the irritability of the detrusor muscle.

The minimal capacity of the bladder is the amount of fill that has collected between the first and second emptying contractions.

The residual urine is best expressed in percentage of fill. To obtain this the amount of residual urine is divided by the sum of the amount of fill (usually 400 cc) and the amount of urine collected from the bladder at zero level at the close of the procedure.

Temporary elevations of intravesical pressure that neither rise to the height of an emptying contraction nor cause leakage about the catheter are aborted emptying contractions.

The presence of an anal or bulbocavernosus reflex is determined last of all. The test is made by prick-

ing either the perianal region or the glans penis with a pin and observing whether or not there is a reflex contraction of the anus. If there is, the reflex is normal, if there is not, it is abnormal.

By plotting the two columns of figures (centimeters of intravesical pressure and cubic centimeters of intravesical fluid) on co-ordinate paper, a graph of the bladder activity during this experimental fill can be drawn. This is not necessary for adequate interpretation, however. Figure 4 depicts the composite result of cystometric data collected as described above from observations on the bladders of normal persons.

Material

This type of cystometer was used to make observations on 50 persons of varied ages and of both sexes who had completely normal nervous systems and genitourinary tracts, 12 otherwise normal women before and after complete presacral-nerve resection for dysmenorrhea, 22 patients with anatomic cord transections, 16 patients with physiologic cord transections, 35 patients with nontransecting cord lesions, 8 patients with injuries to the sacral cord and conus and 20 patients with various degrees of injury to the cauda equina. In addition, there were 50 patients with less severe cord injuries in whom tidal drainage was used for so short a time that the cystometric observations were not considered useful for the purposes of this paper.

The 101 patients in the selected group with injuries to the cord were, for the most part, studied cystometrically at weekly intervals from the time of admission to the hospital until discharge. Correlation was made between the cystometrograms and the presence and condition of any pressure or bedsores that were present. The trend of the serum protein, as measured by weekly observations of the blood level in milligrams per 100 cc, was constantly observed, and a tendency to fall was forestalled, if possible, by a high-protein reinforced diet and if necessary by the transfusion (multiple when indicated) of whole blood. Sepsis of the genitourinary tract was so insignificant a factor¹⁹ after tidal drainage was used efficiently that it had little or no influence on the observations. Other sepsis and toxemia were given due weight when present. At a conservative estimate, over two thousand cystometrograms on 213 patients with various degrees of injury to the cord, conus and cauda equina have been done in the past twelve years. There can be no doubt that the cystometry has complied with the requirements set down above as minimal.

Observations

In addition to observations that have been made on normal human beings, others have been collected from the human analogue of the spinal animal and under physiopathologic conditions that have not

associated with significant injuries of the spinal cord or cauda equina pass through four such stages. These are recognizable only by cystometry and vary unpredictably in duration.

Immediately after injury the bladder is atonic. For this stage the siphon curve should be set at 1 or 2 cm above the bladder level. Recovery progresses through the stages of autonomicity and hypertonicity to the reflex or automatic phase. The siphon curve should be set at 2 to 5 cm above the bladder level for the autonomous, at 15 to 18 cm for the hypertonic and at 10 to 12 cm for the reflex bladder. If the occasion arises—for example, in a patient who is completely unconscious following a severe head injury—when tidal drainage must be used in connection with a normal bladder the siphon curve should be set at 10 to 12 cm above the bladder level, as in the reflex or automatic bladder.

CYSTOMETRY

By cystometry it is possible to determine what the functional activity of the bladder is at the time the cystometrogram is made. As a method of examination it does not pretend to be and cannot be more than relatively exact. If the cystometer and the method of using it approximate as closely as possible the normal physiologic process of filling the human bladder, however, this relative exactitude is sufficient for the purpose at hand. I believe this requirement to be of considerable importance particularly in view of the fact that a number of authors⁷⁻¹⁰ have advocated cystometric methods that do violence to this concept.

A normal bladder that is normally innervated receives urine from the ureters constantly and in small increments.¹¹ The increments are of the order of magnitude of drops. They never, under any circumstances, reach individual amounts of, for example, 10 cc at a time. An increment of 25 or 50 cc is physiologically fantastic. The bladder wall, certainly in human beings and probably also in such animals as the dog and cat, reacts in a physiologically normal manner to any normal increase in content. The musculature can and will react also to the admission at one time of larger amounts of fluid but not in the physiologic manner. Inferences regarding the normal activity of the bladder as the result of such abnormal stimuli are not justified and cannot be accepted as evidence for or against any conclusions other than that a purely experimental procedure that has no physiologic basis produces a certain type of muscular reaction. Conclusions based on such cystometric methods—as advocated by Rose,⁷ Voris and Landes,⁸ Langworthy and Hesser,⁹ and Langworthy, Kolb and Lewis¹⁰—cannot therefore be accepted as explanations of normal bladder physiology. All the authors cited advocate cystometric methods in which unit increments of 25 or 50 cc of fluid are repeatedly introduced into the bladder.

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patient can tell whether his bladder is empty and needs to be emptied may be misleading to determine at what point desire to void occurs and at what point pain occurs. The first is a function of the patient's ability to inhibit emptying contractions and is affected by such a wide variety of stimuli — varying from inability to urinate while in bed or in the presence of another person to the effect of a total

those advanced in the two previous papers^{5, 20} of this series are compiled from observations made on human beings only. Lesions of the spinal cord have been verified by operation, autopsy and clinical observations carried on for a sufficiently long time to establish a stabilized end point and the diagnosis beyond any question of doubt. Cystometrograms have been made in accordance with the physiologic requirements outlined above and by a wide variety

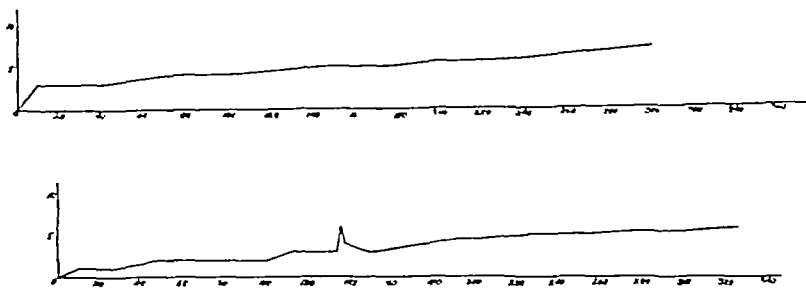


FIGURE 5 The Graphs of Atonic Bladders

The upper one was made ten hours after a cervicodorsal hematomyelia, and the lower one forty-three days after a cervical hematomyelia. In the latter case the atonicity occurred following the development of a major infection.

d transection — that conclusions based on it are not only unreliable but may lead one astray. The sensation of pain in the bladder wall, if present, means that the organ is being dangerously over-stretched. If not present, it may mean the same thing only this time that the danger will be greater

of observers. They strongly suggest the following conclusions. When a human spinal cord is transected either anatomically or physiologically below the fourth cervical and above the second sacral segment, in addition to a complete anesthesia and a total loss of all voluntary motor control below the

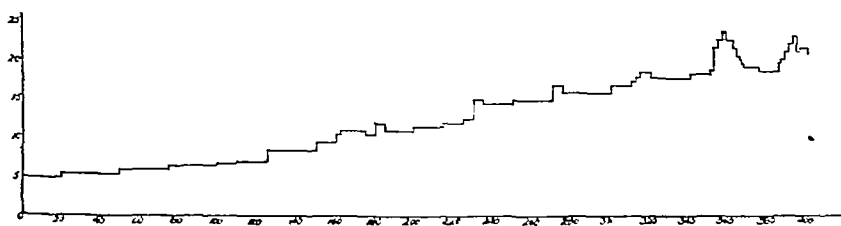


FIGURE 6 The Graph of an Autonomous Bladder

This measurement was made twenty-three days after concussion with transection of the dorsal cord. Aborted emptying contractions are present.

because it is unrecognizable. In addition, it may be pointed out that any interpretations of the physiology of micturition that depend even in part on observations made by the patient and that require an intact nervous system are valueless in the face of an anatomically or physiologically transected spinal cord. The observer who is accustomed to rely on such observations in his clinical work will find himself without them and at a loss in the type of case in which he needs cystometrography most.

The interpretations presented herewith as well as

level of cord injury, the immediate response of the bladder is to become atonic (Fig 5). The detrusor muscle does not contract at all. The internal sphincter closes tightly and remains closed and unresponsive to any physiologic stimuli during this phase. The external sphincter is relaxed, and the anal and bulbocavernosus reflexes are abolished. Any emptying that occurs is only the result of leakage through the contracted internal sphincter and takes place because of the elasticity of the bladder wall and not by virtue of any contractile effort on its part. The

previously been duplicated. The effects of sepsis, hypoproteinemia, avitaminosis, anemia, physical activity and the like have all been evaluated in relation to the problems of the physiology of micturition and the recovery of the bladder function in these patients. Complications that under other conditions and in other similar series of observations have altered, made unreliable and in some cases vitiated the observers' conclusions either have been recognized as untreatable and the conclusions discarded

the curve of basic tonus, varying from the flat curve of atonicity to the steep gradient of hypertonicity—the former may be present in normal bladders and will be present between the emptying contractions in reflex bladders, and the latter occurs as described below, an anal or bulbocavernosus reflex, which is present only in the absence of spinal shock and when the internal pudic nerve and its spinal-cord connections are intact, indicating either normal voluntary or abnormal involuntary reflex control of the ester

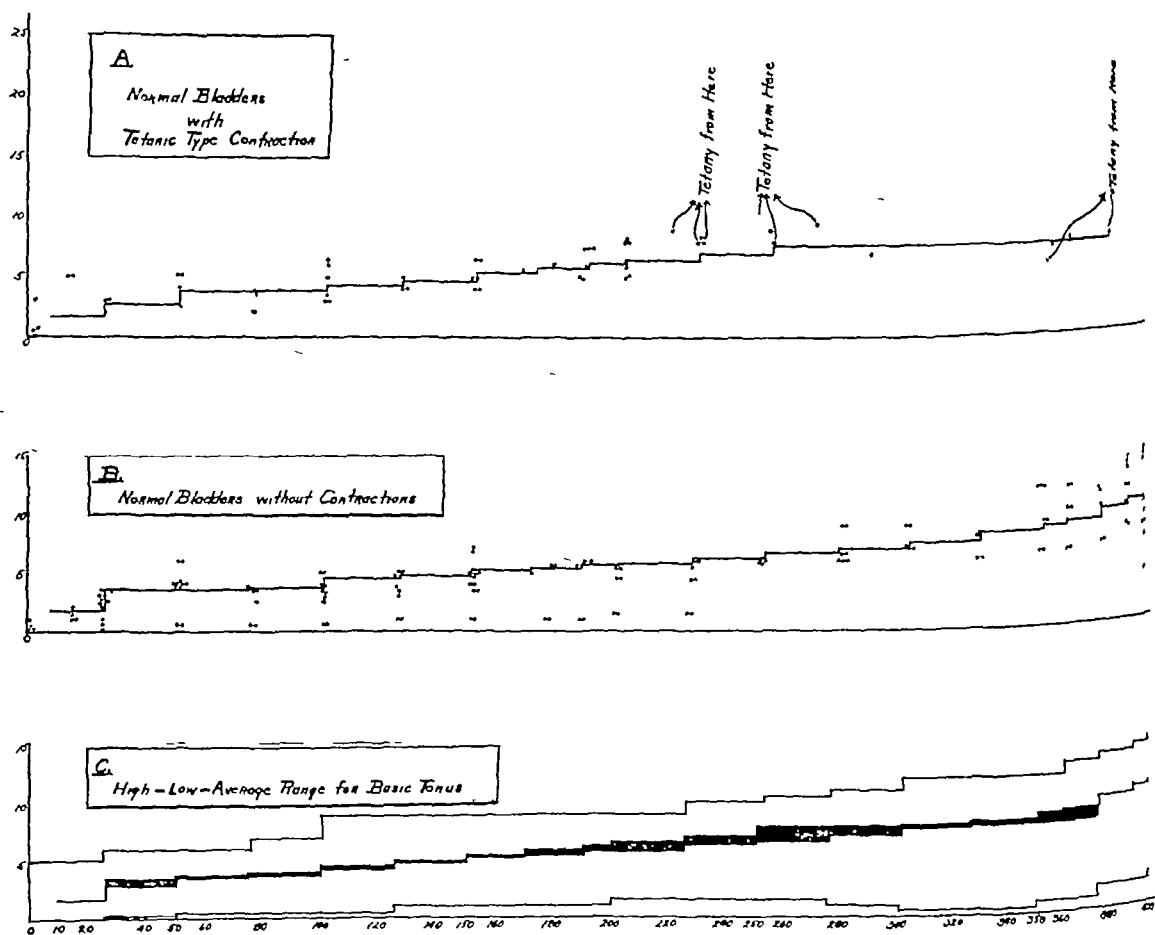


FIGURE 4 Composite Cystometric Data Relative to the Normal Bladder
On the abscissas are recorded cubic centimeters of fill, and on the ordinates centimeters of pressure

or have been successfully treated and brought to an end before conclusions were drawn. In the course and partly as the result of these observations it became apparent that in interpreting this group of cystometrograms certain information was essential, other data were not essential but possibly useful, and some were misleading in an estimation of the degree of recovery of bladder function. The essential cystometric information is as follows: the presence of emptying contractions—only normal or reflex bladders develop the classic emptying contractions,

nal urethral sphincter, and the capacity of the bladder, which will be a minimal figure varying from the large amount that is limited only by the elasticity of the bladder wall and is collected in atonic bladders to the small amount that is present in bladders that are hypertonic, hypertrophied and shrunken or infected—a minimal capacity below 150 cc is abnormal.

It is useful to know whether or not aborted emptying contractions are present, how much residual urine (expressed in percentage of fill) is present, and

the control that is apparent later as normal micturition. Under certain conditions, however, this inhibitory ability can be lost again, the bladder reverting to reflex activity in the absence of any physical impairment of its nervous connections. Emotional stress, such as extreme fear or bodily harm, may so relax the inhibitory control exerted by the higher centers that the person experiencing such an emotion finds himself — if the bladder has not been emptied just previously — voiding urine once the danger is passed. I am inclined to think that this was not an infrequent experience during the worst London air raids. Coma, if suffi-

cient to produce overflow incontinence is the result of an inhibitory effect exerted to the point of overdilatation and caused by a subconscious realization that bed is not the place in which to urinate. The restlessness and struggles to get out of bed that persist until a urinal is put in place and the bladder emptied completely of a large amount of urine, only to be followed by a period of quiet or sleep, afford verification of this phenomenon. Indeed, the change from the periodic urination of large amounts that is characteristic of reflex micturition to the irregularly spaced, frequent discharge of the small amounts of overflow incontinence is often an early and always a reliable sign

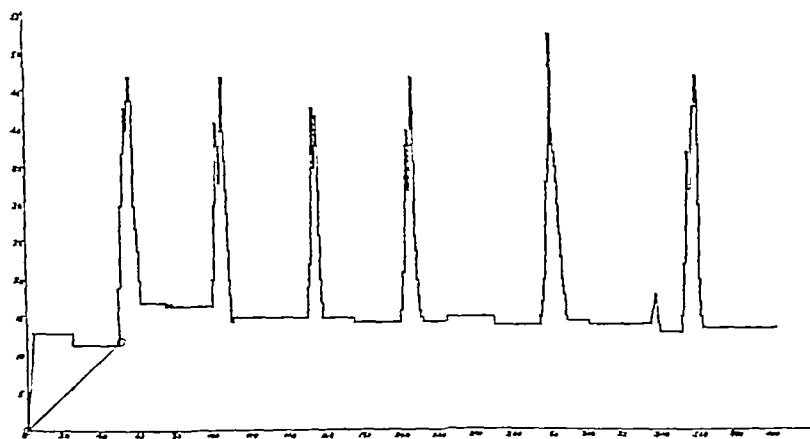


FIGURE 8 *The Graph of a Reflex Bladder*

This measurement was made seven months after concussion with transection of the dorsal cord

ciently deep, produces the same chain of events, if it is less profound, and even though the victim is out of conscious touch with his surroundings, inhibitory control continues to be exerted, however, and the bladder is prevented from emptying. Convulsive seizures with the profound coma and loss of "sphincter control" of grand mal, on the one hand, and the momentary unconsciousness without soiling of the petit-mal attacks, on the other, as well as the variations between, illustrate these phenomena in all degrees.

Cerebral injuries, although not so clear cut on account of the associated central-nervous-system damage, provide similar examples. The deeply comatose patient empties the bladder of large amounts of urine at rare, fairly evenly spaced intervals. The bladder functions on a pure reflex plane, empties completely with each emptying contraction and is deprived of all inhibitory influences. As the condition improves and the coma lessens, the type of micturition changes, and the patient begins to pass small amounts of urine often and at irregular intervals. Catheterization easily demonstrates that

of the lessening of unconsciousness and an improvement in such a patient's condition and vice versa.

Reflex bladder activity is also a function of the anatomically and physiologically transected cord. Under such conditions, it is the best end result that can be attained, and bladder training as described below is merely a method of making practical use of this phenomenon. It is this activity that has been referred to in the past as the "automatic bladder." In nontransecting injuries, it is not and should not be considered an end result. In these injuries the activity is analogous to that of the reflex bladder of the normal infant. Further training enables the patient to regain the normal inhibitory control just as the child does as he grows older. In this reflex stage the detrusor muscle contracts reflexly and completely in response to the sensory stimulus provided by the stretch of a critically filled bladder. During the fill and before the accumulation of this critical amount of urine, any emptying contractions are aborted in favor of a stretch reflex and consequent increase in the cubic capacity of the organ. The internal sphincter remains closed until the emptying

bladder capacity is limited only by this elasticity. Bladders that have advanced beyond this stage toward recovery will regress to it in the presence of spinal shock, exhaustion, sepsis, toxemia and hypoproteinemia (Fig 5). The length of time that a bladder remains in this atonic stage depends on these complications, the severity of the injury and the efficiency of the treatment.

The next stage toward recovery is characterized by the development of ineffective aborted emptying contractions (Fig 6). The level of basic tonus is slightly higher than that in an atonic bladder. The internal sphincter is tightly closed and only partially

but not proved that the neural control is exerted, way of an intramural autonomous plexus.

The third stage toward recovery is the hypertonic. This is characterized by something approximating tetany of the detrusor muscle (Fig 7). It is in a nearly constant state of contraction, the curve of basic tonus is steep, and the intervals between emptying contractions are extremely short. The internal sphincter reacts physiologically, opening with each emptying contraction and closing in the intervals. The external sphincter responds reflexly, and the anal and bulbocavernosus reflexes are present. The bladder capacity as measured by the amount

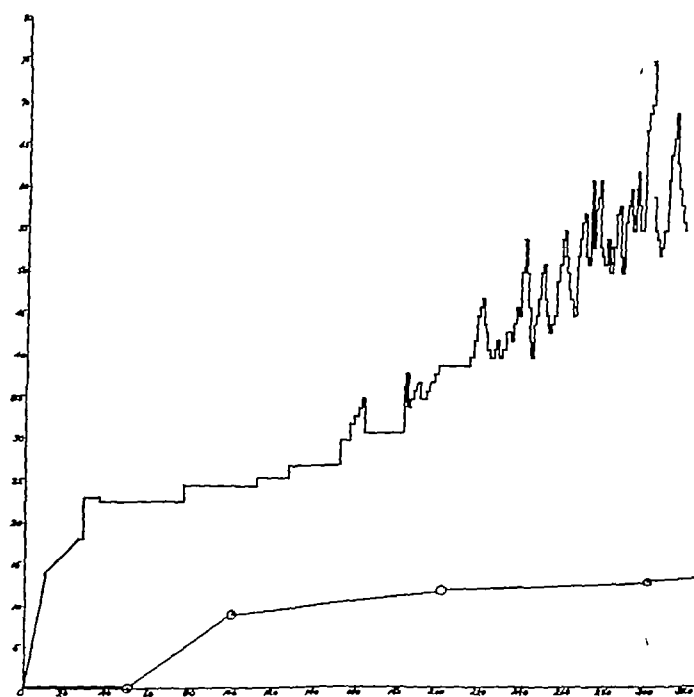


FIGURE 7 The Graph of a Hypertonic Bladder

This graph was made five days after compression of the lumbosacral cord

opens in response to the inefficient aborted emptying contractions of the detrusor muscle. The bulbocavernosus and anal reflexes may return. There are no emptying contractions. This stage may be extremely short and will be missed if cystometrograms are not made frequently enough. The bladders discharge small amounts of urine frequently. Their capacity is at first large but becomes increasingly smaller as hypertrophy of the muscular wall develops. The bladders regress to the atonic stage for the reasons given above. The length of time that the bladder remains in this stage again depends on any complications and the efficiency of treatment, but not on the severity of the injury. This is the autonomous stage, so called because it is believed

of urine stored between emptying contractions is small. This stage is often of short duration; either it regresses toward atonicity or progresses to the reflex stage. An acutely infected but otherwise normal bladder may give a cystometrogram that is indistinguishable from one made during this stage. Normal uninfected bladders exhibit these characteristics just before emptying if they are distended beyond normal limits but have not been so stretched as to have become atonic (Fig 4).

The final stage is that of the reflex bladder (Fig 8). In small children who have not yet learned to obey the dictates of civilization this represents normal bladder activity. Increase in capacity and training in the inhibition of emptying contractions pro-

he bladder concerns the transmission of pain that organ appears to be confirmed

BLADDER TRAINING

Bladder training should be necessary only in patients with anatomically or physiologically transected cords. It will be effective only if the patient has an intelligent interest in the problem and co-operates. If the bladders have been properly cared for from the time of injury, such training is not necessary with nontransecting cord injuries. It is ineffective in patients with destructive lesions of the spinal cord or roots and the parasympathetic centres. It cannot be imposed on and is not successful in any patient who is mentally deficient or inco-operative or who has a suprapubic or perineal stoma, bladder obstruction from any cause, an infected bladder, vesical or renal calculi, pyelitis or pyelonephrosis, general sepsis, toxemia, exhaustion, debilitation, hypoproteinemia, avitaminosis, large unhealed bedsores and the like. The bladder activity must be of the reflex type, and the bladder capacity at least 200 cc, in patients with an active mass reflex the lower half of the abdominal wall must have been paralyzed either because of approximate thoracic-root destruction as part of the injury or following operative bilateral anterior dorso-lumbar rhizotomy. To prevent genitourinary infection the fluid intake must not be allowed to fall below 3600 cc in twenty-four hours during the period of training. Bladder training is much easier when the patient is ambulant in splints and with the aid of crutches, but its initiation should not be postponed on that account. The patient must have sufficient use of his hands to clamp and unclamp the catheter, must have a watch, must understand the elements of the problem he is faced with, must be co-operative and must be willing to assume full responsibility for the solution of that problem. With these requirements met, all that is necessary is patience and perseverance on the part of both the patient and the doctor.

Control of micturition is possible in the presence of a transected cord because the bladder, if not otherwise altered, can be distended to a point where it contains from 200 to 400 cc of urine before emptying and because an emptying contraction can be initiated as a reflex response to appropriate sensory stimuli at any time previous to that point. By appropriate regulation of the fluid intake, the time that elapses before this amount is collected in the bladder can also be predetermined. By emptying the bladder reflexly under controlled conditions immediately before the contents reach the critical level, soiling with urine at unexpected times can be prevented.

Technic

The first stage in the training is to condition the bladder so that it will distend to the point where it

holds 200 cc or more without developing an emptying contraction. This phase can and should be started while the patient is still in bed and as soon as the bladder activity has become reflex in type. To do this, the catheter is left in place but disconnected from the tidal-drainage apparatus and clamped off for an hour and a half at a time. At the end of each of these periods the catheter is opened, the open end placed so as to empty into a urinal and the bladder made to contract by appropriate reflex stimulation such as massage of the abdomen, scratching of the thigh or any similar procedure that is effective. Forcible expulsion of the contents by pressure through the abdominal wall should not be practiced under any circumstances. The fluid intake is adjusted so that no fluid is taken between 7:00 p.m. and 7:00 a.m. During the other twelve hours 300 cc should be ingested every hour, preferably on the hour. This fluid intake remains the same throughout the training period and thereafter until full adjustment and control are obtained. The patient should be held responsible for draining his own bladder at proper intervals during the day. At night the catheter should be attached to the tidal-drainage apparatus. After he is able to go for a week without leakage between emptyings, the interval should be increased to two hours. The process is repeated until the same requirement can be successfully met. After this, the interval is increased to two and a half hours and then to three hours. The greatest difficulty is usually encountered in making the change from an hour and a half to two hours. If leakage occurs at that time or at any other change, the patient should be put back on the next shortest interval for another week or so and the shift upward tried again.

When the patient can successfully manage a three-hour interval without leakage, he should be taken off tidal drainage at night. Instead he should be awakened and made to empty the bladder every two hours until a week has passed without leakage and subsequently every three hours. He will then be able to retain the bladder contents for three hours at a time without leakage day and night, but the catheter will still be in place. The activity of the detrusor muscle has been conditioned, but not the sphincters. To attain that end, the catheter should be removed entirely and the time interval between emptyings cut back again to an hour and a half. The intervals are then increased as indicated above, but without the catheter. It is during this stage that obstruction by a spastic or hypertrophied internal sphincter becomes evident if it exists. Such a condition occasionally requires resection, but this should not be done until a serious effort has been made and enough time allowed to elapse for the sphincter to correct its own spasticity. Any other obstruction to emptying must be corrected at once and before the training can be continued. It is about this time also that the patients begin to be ambulant. This

contraction takes place, when it opens and permits urine to escape into the posterior urethra. This, in turn, acts as a sensory stimulus that causes the external sphincter to relax reflexly from its previously contracted closed position. The bulbocavernosus and anal reflexes are present. If the cord injury is nontransecting the patient also has the ability to relax and contract voluntarily the external sphincter. If the injury is a transecting one, this voluntary control is permanently lost. If the bladder has not been allowed to shrink during the early stages of its recovery from atonicity, its critical capacity varies from 200 to 400 cc or more. When it does empty, all the contents are expelled. Reflex emptying in cases of transected cord may also be initiated — regardless of the amount of the contents — by contraction of the abdominal muscles, stimulation of the abdomen, thigh and other areas of the leg, catheterization, movement of the bowels and change in position. Facilitation of micturition as a part of the "mass reflex" described by Head¹⁶ is, according to my observations, no more than an indirect and coincidental effect. In patients whose abdominal musculature has been paralyzed because of the destruction of the lower dorsal roots but in whom the mass reflex is typical and active, there is no such facilitation. I have seen two such cases. Also, as noted in a previous paper,²⁰ in patients in whom the mass reflex has been inactivated by anterior rhizotomy, facilitation of micturition is still present on a reflex level in response to stimulation of the skin of the thigh and an increase in intra-abdominal pressure, as well as to intravesical stimulation acting alone and without any external aid and caused by the collection of a critical amount of fill within the bladder. I have had experience with 10 such cases. Regression toward atonicity takes place in the presence of infection, toxemia, exhaustion, a major operative procedure, hypoproteinemia and so forth. A decrease in capacity and hence an increase in the number of emptying contractions develop in the presence of cystitis, vesical calculi and prolonged suprapubic drainage. Urinary retention despite the presence of otherwise efficient emptying contractions has been shown to be caused by hypertrophy or fibrosis²¹⁻²⁴ with a pseudo-median-bar formation of the internal sphincter. Although the evidence is not conclusive, it is probable that this retention has its origin in injudicious early treatment of the bladder and is a complication of too prolonged and constant catheter or suprapubic drainage. It has occurred only twice in my series of 40 cases with anatomic and physiologic transections. One was in a patient who had been subjected to suprapubic drainage for five months followed by catheter drainage for the same length of time. The other had catheter drainage for three months following the accident. For two years and nine months thereafter he had no bladder treatment of any kind. Many of the other patients in this group, however,

had as long or longer periods of suprapubic or catheter drainage without the development of this complication.

Destructive lesions that are complete and involve the sacral segments or roots or the parasympathetic plexuses, and hence completely denervate the bladder as far as its central connections go, force the bladder to depend on the intramural plexus for neuromuscular control. This ability develops after the bladder has recovered from the atonic stage. The resultant bladder activity duplicates that described above under the term "autonomous bladder" (Fig. 6). This is the best physiologic end result that can be obtained in such cases. Because of the total denervation it is impossible to impose bladder training on these patients. That does not mean, however, that the patients must accept a contracted bladder that will hold only 30 or 50 cc and that leaks continually constantly. Even in the face of total denervation, the bladder capacity can be maintained at normal by the prompt use of tidal drainage in the preconvalescent bed stage. When the patient is ambulant, unailing twenty-four-hour control can be established if the patient continues to wear an indwelling catheter. During the day the catheter is kept closed by a clamp except when the bladder is emptied at intervals of three or four hours. During the night, while the patient is in bed, the catheter is opened and attached to a tidal-drainage apparatus with the siphon curve set at 10 to 12 cm. The bladder wall is thus kept from hypertrophy and contraction, and the patient is enabled to keep himself dry and clean at all times. The catheter is removed, cleaned, resterilized and replaced aseptically once a week, and the apparatus taken down, cleaned, resterilized and reassembled after the same interval. Solution M or Solution G⁶ is used as an irrigating fluid. Any person of ordinary intelligence can without difficulty be taught the proper care of himself and this apparatus.

Impulses reaching the bladder by way of the sympathetic as distinguished from the parasympathetic and somatic nervous systems have no influence on the function of storage or discharge. This was first enunciated by Denny-Brown and Robertson.²⁵ Through the kindness of Dr. Frank A. Pemberton I was enabled to make preoperative and postoperative cystometric observations on 12 otherwise normal women whose presacral plexuses were totally removed because of dysmenorrhea. In every case the bladder activity was unaltered following the sympathetic denervation. Similar findings have been reported by Marshall and Kennedy.²⁶ In the light of this evidence, Learmonth's²⁷ conclusions, and Fulton's¹⁷ acquiescence in them, regarding the antagonistic control of bladder activity so far as it refers to the sympathetic-nervous-system innervation of the bladder, cannot be accepted any longer. Denny-Brown and Robertson's²⁵ original contention that the effect of the sympathetic nervous system

not investigated but not even considered, this is permitted to remain undisturbed only to minimize and produce fibrotic adhesions, which compress and deform the cauda equina.²⁸ Varied symptoms of radiculitis develop, the usual ones being alone or in combination with the type of urinary difficulty described above. Clinical evidence suggests that to correct the bladder symptoms the radiculitis must be relieved and the bladder stretched if it has shrunk. The first is accomplished by a decompressive lumbar laminectomy in which the five laminae overlying the cauda equina are removed, the dura opened for the full length of the wound and any neurolysis that may be possible carried out. The wound is then closed without drainage and without closing the dura. Preoperative investigation of the dynamics of the spinal cerebrospinal fluid is essential and usually reveals a partial and often a complete dynamic block. The patient is put on tidal drainage adjusted to meet the requirements of the cystometric findings and to stretch the bladder if necessary. This is continued until the capacity has been raised to over 200 cc, after which bladder training as described above is instituted. Following this procedure, which has been carried out in 14 such patients, all of whom were unemployable on account of their urinary difficulty, all but 2 have returned to regular employment and all are free of urinary symptoms.

SUMMARY

Two types of apparatus for tidal drainage are described, and directions given for their construction. The physiology of micturition is briefly discussed. A method of cystometric examination of bladder function in normal bladders and in those rendered abnormal by spinal-cord, conus and cauda-equina injuries is described, and an interpretation of the findings is given. A method of bladder training that will permit unfailing twenty-four-hour control of urination, even in the face of an anatomic cord transection or total denervation of the viscus, is discussed in detail.

REFERENCES

- 1 Munro, D and Hahn J. Tidal drainage of urinary bladder: preliminary report of this method of treatment as applied to cord bladders with description of apparatus. *New Eng J Med* 212: 229-239 1935
- 2 MacNeill, A. E., and Bowler J. P. Irrigation and tidal drainage. *New Eng J Med* 223: 128-132 1940
- 3 Stewart O. W. Neurogenic bladder: combined tidal irrigator and cystometer. *Lancet* 1: 287-289 1942
- 4 Cone W. V., and Bridgers W. H. Combined tidal irrigator and cystometer for management of paralyzed bladder. *Surg Gynec & Obst* 75: 61-66 1942
- 5 Munro D. Rehabilitation of patients totally paralyzed below waist with special reference to making them ambulatory and capable of earning their own living. II. Control of urination. *New Eng J Med* 234: 207-216 1946
- 6 Suby H. L. and Albright F. Dissolution of phosphatic urinary calculi by retrograde introduction of citrate solution containing magnesium. *New Eng J Med* 228: 81-91 1943
- 7 Rose D. K. Determination of bladder pressure with cystometer: new principle in diagnosis. *J A M A* 88: 151-157, 1927
- 8 Voss, H. C., and Landes H. E. Therapy of neurogenic bladder. *J Internat Coll Surgeons* 5: 206-215, 1942
- 9 Langworthy O. R. and Hesser F. H. Experimental study of micturition released from cerebral control. *Am J Physiol* 115: 694-700 1936
- 10 Langworthy O. R. Kolb L. C. and Lewis L. G. *Physiology of Micturition. Experimental and clinical studies with suggestions as to diagnosis and treatment*. 232 pp. Baltimore: Williams and Wilkins 1940
- 11 Starling E. H. Muscular mechanisms of urinary tract. In *Text Book of Physiology*. Edited by E. A. Schäfer. Vol. 2. 1365 pp. Edinburgh and London: Pentland 1900. Pp. 338-347
- 12 Munro D. "Cord bladder": its definition, treatment and prognosis when associated with spinal cord injuries. *J Urol* 36: 710-729 1936
- 13 *Idem*. Treatment of urinary bladder in cases with injury of spinal cord. *Am J Surg* 38: 120-136, 1937
- 14 *Idem*. Care of back following spinal-cord injuries: consideration of bed sores. *New Eng J Med* 223: 391-398 1940
- 15 *War Department Technical Bulletin*. No 162. May 1945
- 16 Head H. and others. *Studies in Neurology*. 862 pp. Vol. 2. London: Henry Frowde 1920
- 17 Fulton, J. F. *Physiology of the Nervous System*. Second edition. 614 pp. New York: Oxford University Press 1943
- 18 Munro D. Activity of urinary bladder as measured by new and inexpensive cystometer. *New Eng J Med* 214: 617-624 1936
- 19 Badal D., Munro D. and Lamb M. E. Clinical significance of bacteriuria in patients with spinal-cord injuries. *New Eng J Med* 230: 688-693 1944
- 20 Munro D. Rehabilitation of patients totally paralyzed below waist with special reference to making them ambulatory and capable of earning their own living. I. Anterior rhizotomy for spastic paraplegia. *New Eng J Med* 233: 453-461 1945
- 21 Pierson E. L. Transurethral resection of internal sphincter in certain type of cord bladder. *New Eng J Med* 213: 50-54 1935
- 22 Van Duzen R. E. Operations for urinary control of neurogenic bladders. *J Urol* 53: 565-571 1945
- 23 Band D. Cystometry. *Brit. J Urol* 17: 1-25 1945
- 24 Lewis L. G. Discussion of Hanlon R. E. Treatment of urinary incontinence in vesical paralysis. *J Urol* 53: 572-579, 1945
- 25 Denny-Brown, D. and Robertson E. Graeme. On physiology of micturition. *Brain* 56: 149-190 1933. State of bladder and its sphincters in complete transverse lesions of spinal cord and cauda equina. *Ibid* 56: 397-463, 1933
- 26 Marshall S. F. and Kennedy, R. J. Postoperative results following presacral neurectomy (excision of hypogastric plexus) for dysmenorrhoea. *S Clin North America* 25: 518-529 1945
- 27 Learmonth J. R. Contribution to neurophysiology of urinary bladder in man. *Brain* 54: 147-176 1931
- 28 Munro D. Treatment of patients with injuries of spinal cord and cauda equina: preliminary to making them ambulatory. *Clinics* 4: 448-474 1945

change from the recumbent or sitting to the erect position also alters the bladder activity. It is often found that control of micturition, which is entirely satisfactory with the patient erect, fails miserably when he returns to bed. Increased exercise, such as greater agility in using crutches, may also cause temporary intermittent leakage. Persistence in practice and repetition of the earlier training stages, even perhaps to the extent of catheter replacement, will overcome all these difficulties sooner or later, particularly if an increase in ambulation is insisted on. It is also helpful if the patient makes a practice of using the toilet rather than the urinal at each bladder emptying. The position of the body and possibly also the psychology of urinating in such surroundings appears to be conducive to greater efficiency in micturition. In especially difficult cases much help can often be obtained by making the patient keep his own intake and output chart. This should include a time schedule as well.

Complications

Once the patient has reached the stage where he can go for three hours without urinating or leaking during both day and night, he can be allowed to go through the night without being awakened at all or, at most, only once. The daytime interval can also be extended from half an hour to an hour if the need arises. Under no circumstances should the interval between drainages be shortened — such a procedure will quickly cause regression of bladder function. Any unexpected break in efficiency should lead to prompt investigation of the cause. One of my patients was found to have a vesical calculus that had been entirely asymptomatic until the patient was well past the first stages of ambulation. Sudden inability to control micturition in another case was found to have been caused by a small papilloma that had developed without my knowledge and in spite of previous cystoscopic examinations while the patient was under treatment for a cord injury. Removal of the stone and fulguration of the papilloma permitted both patients to regain twenty-four-hour control of micturition.

Successful bladder training can be acquired by any patient with a transected cord if the requirements discussed above are met. It is acquired much more easily and rapidly, however, if the bladder is kept in a state of physiologic normalcy during the immediate post-injury convalescence by the proper use of tidal drainage supplemented by the necessary number of cystometrograms. As pointed out above, an automatic bladder, although better than a contracted or permanently drained bladder, cannot be considered a satisfactory end result. It is merely a preliminary stage in the return of bladder function and should be recognized as a condition that can be transmuted into unfailing twenty-four-hour control of micturition if the physician is alert

to the possibilities and the patient intelligent co-operative.

Patients with denervated bladders (destructive lesions of the sacral cord or roots or parasympathetic plexuses) can have the same control but must be willing to wear a catheter constantly and to maintain tidal drainage at night. They are trained in the manner described above to increase the interval between bladder drainages from an hour and a half to three hours, except that they never reach the stage of training without catheters and that they are not awakened at night. It is possible that resection of the internal sphincter²¹ will eventually prove to be the solution that will permit removal of the indwelling catheters and abandonment of the tidal-drainage apparatus in these cases.

No satisfactory method of treating the urinary difficulties of patients with paralyzed hands has been evolved, other than to have an attendant open and close the catheters during the first part of the training period. Manpower shortage has made this impractical, but if that difficulty can be overcome, there is no reason why such patients should not eventually attain bladder control once the catheters can be removed. After that, the reflex emptying that follows sensory stimuli set up by scratching the abdomen or thigh will be within the scope of their limited activities. Fortunately, these cases are rare, because patients with transections of the middle and lower thirds of the cervical cord — whether anatomic or physiologic — rarely survive long enough to reach the stage where bladder training is indicated, and if they do, it is of little practical value to them because of the impossibility of ambulation. So long as they are bedridden, they do better on tidal drainage. Patients with nontransected cases with hand paralysis traceable to cord changes associated with hematomyelia will have normal bladder activity if their bladders are properly treated from the start. The only problem is to obtain urinals that they can use when necessary. With normal control of micturition, accidents can usually be avoided because of the leeway permitted by virtue of the ability to inhibit an emptying contraction for a reasonable and possibly a considerable period.

Patients with cauda equina injuries that do not denervate the bladder may nevertheless have sufficiently disabling bladder symptoms to prevent a normal social and work life. Cystometrically, the only variation from normalcy is a decreased capacity and evidence of hypertonicity in that emptying contractions develop more frequently than normal and the curve of basic tonus is steeper than normal. The bladder symptoms are usually extreme urgency, frequency, dribbling and unexpected major leakage. In my experience all these patients have sustained such injuries in civil life. There has been a major fracture of a lumbar vertebra with the escape of quantities of free blood into the lumbar subarachnoid space. Because this possibility is usually no

underwent a second operation, during which 83 of tissue was removed. The postoperative course difficult, with true thyroid storm, and again the ase persisted until the final operation, when 50 of tissue was removed. Following this, except a transient unilateral vocal-cord paralysis, this patient made a complete recovery.

Thompson and his colleagues^{2,3} have presented much of the adequate data on recurrent and persistent hyperthyroidism, reporting an incidence of operative thyrotoxicosis in 19.5 per cent of cases at the Massachusetts General Hospital and in 17.5 per cent at the Presbyterian Hospital in Chicago. Data from the Massachusetts General Hospital indicate that this rather high incidence was attended by a low incidence of true myxedema (1 per cent). The studies made in the series at the Peter Bent Brigham Hospital reveal that 83 per cent of patients avoided recurrent or persistent thyrotoxicosis.

The figures cited above indicate that the results reported from the Peter Bent Brigham Hospital are probably representative of those to be expected from other hospitals where general surgery is practiced. They are also in accord with the data concerning postoperative thyrotoxicosis gathered by Fulton, Smith and Cutler⁴ in this hospital in 1938.

Four patients died as a result of the operation. The ages ranged from forty to forty-nine years. Two deaths were due to postoperative thyroid storm, and one to hemorrhage into the wound with cessation of respiration. Each of these patients had responded favorably to treatment with iodine and bed rest prior to operation. The fourth fatal case occurred in a woman who refused further treatment after an adequate response to iodine had been obtained. She continued to take iodine for ten months after discharge and lost 35 pounds in weight. After readmission to the hospital, where iodine was withheld for three weeks, she failed to respond when it was readministered. The patient died on the operating table. Microscopically, the thyroid gland showed "diffuse hyperplasia with iodine involution," and in addition, a diagnosis of acute rheumatic fever was made at autopsy. This case is an example of the recognized clinical phenomenon that surgery is safest when it follows iodine therapy given patients for the first time, or when such patients have been untreated by iodine for at least six to eight weeks before operation.

A comparison of these results with those reported from other institutions is of interest. Mortality statistics in thyroidectomy for Graves's disease vary greatly, ranging as high as 13.1 per cent, as reported by Thompson, Taylor, and Meyer⁵ at the Cook County Hospital. Maes, Boyce, and McFetridge⁶ reported a mortality of 10.6 per cent at Charity Hospital in New Orleans. Among the lowest figures is that of 0.63 per cent given by Clute.⁷ It appears that the surgical mortality in Graves's disease at the Peter Bent Brigham Hospital (2.7 per cent) is

in the lower range for hospitals in which general surgery is practiced.

A final compilation may be made by a division of the cases into two groups — those with satisfactory and those with poor results.

To the 80 patients who experienced a return to complete good health may be added the 18 patients with hypothyroidism, since all ultimately became asymptomatic through the use of thyroid. In addition, the persistence of exophthalmos should not be considered a poor result, and 10 patients in whom this occurred as a single complication can be added to those with satisfactory results. The seriousness of unilateral vocal-cord paralysis is probably best evaluated in terms of the subsequent course. In 3 patients this occurred as a single complication, and because the later course was quite satisfactory, they can also be added to those with acceptable results. This number can also be supplemented by 2 patients who had temporary tetany. Thus, 113 patients, or 87 per cent, of the 130 followed for a minimum of six months are considered to have had a satisfactory outcome.

The 11 patients who suffered a recurrence or persistence of thyrotoxicosis, the 1 with permanent parathyropria, and 1 of those with vocal-cord paralysis should be regarded as having had unfavorable results. The case of vocal-cord paralysis is so classified because a unilateral injury occurred during the first stage of an intended two-stage procedure, and the patient refused further treatment because of this complication. In addition to these complications among the 149 patients subjected to operation, 4 deaths occurred. Thus, unsatisfactory results were obtained in 17, or 13 per cent, of the 130 cases that were adequately followed.

The data in the surgical treatment of Graves's disease (Table 1) indicate that 113 of the 130 pa-

TABLE 1 *Results of Surgical Treatment in 130 Cases of Graves's Disease*

RESULT	PERCENTAGE
Satisfactory	
Return to good health	61.5
Hypothyroidism (single complication)	13.9
Exophthalmos (single complication)	7.7
Unilateral temporary vocal cord paralysis (single complication)	2.3
Temporary tetany	1.5
Total	87
Unsatisfactory	
Persistent or recurrent thyrotoxicosis	8.5
Permanent parathyropria	0.8
Vocal cord paralysis at first stage operation	0.8
Death	3.1
Total	13

tients followed are known to have had results that permitted a return to a normal life, and 13 had complications of some severity, mostly permanent in nature. Four patients did not survive the operation. Nineteen patients did not keep in touch with the hospital, so that a complete history of their cases is not a matter of record. It is also realized that a

THE RESULTS OF SURGICAL TREATMENT IN GRAVES'S DISEASE*

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THE introduction into this clinic by Astwood¹ of thiouracil and other potent antithyroid drugs for the medical treatment of Graves's disease resulted in a challenge to the concept that this condition is best treated surgically. Thus, there is a growing divergence of opinion concerning the relative merits of medical and surgical therapy in hyperthyroidism.

As a contribution to the discussion of this problem, a study has been made of the results of surgery for a period during which the performance of adequate subtotal thyroidectomy, combined with the proper use of iodine and other preoperative and postoperative measures, was the accepted method of therapy. This study is a review of all the cases of Graves's disease—that is, toxic diffuse goiter—surgically treated at the Peter Bent Brigham Hospital from 1933 through 1940. In the eight years reviewed, operations were performed in 149 cases in which a pathological report of diffuse hyperplasia of the thyroid gland was made. It is believed that such an analysis will establish a pattern against which similar controlled observations on patients treated with thiouracil may be compared.

It is the practice of the Surgical Service to follow these patients at regular intervals, and a majority of them were seen in the follow-up clinic of the hospital over a period of several years. For the purpose of this analysis, no result was considered satisfactory unless the patient had been under observation for at least six months after operation. When an unsatisfactory result was immediately apparent, however, this has been indicated, even though the patient's condition could not be checked through a minimum of six months. Nineteen patients whose condition at discharge was satisfactory failed to maintain contact with the clinic for a sufficient length of time to allow their final status to be evaluated.

Hypothyroidism after thyroidectomy was encountered in 18 cases. In 9 of these the classic signs of myxedema were found, the metabolic rate in 7 cases ranging from -31 to -47 per cent. The other 9 patients suffered from mild hypothyroidism. In all these cases the condition was well controlled with the administration of thyroid, and the patients eventually led useful and comfortable lives.

Vocal-cord paralysis was noted immediately following the surgical procedure in 7 cases, in 3 of which it was a single complication. In 1 case, which occurred after a first-stage hemithyroidectomy, the patient refused the second stage. Six patients had temporary unilateral paralysis on the basis of symptoms and postoperative examinations.

Four patients showed symptoms of hypoparathyroidism. In one there was evidence of permanent parathyropriav, on the basis of symptoms and of blood calcium and phosphorus levels. This patient was symptomatically controlled on vitamin D. The case was unusual in that preoperatively tetany could be induced by hyperventilation. One patient was followed for two months, at the end of which he had recovered from the tetany and did not return to the clinic, in addition to mild hypoparathyroidism, this patient sustained a vocal-cord paralysis and mild hypothyroidism. The third patient apparently suffered only a partial parathyroidectomy, since the symptoms of tetany disappeared five days after the operation. The fourth patient lost all signs of tetany within six months and continued in good health for at least eight years.

Persistent exophthalmos was observed in 13 cases. In only one of these did progression of the exophthalmos occur, and the patient was treated by the Naffziger procedure. One patient had marked unilateral, and one marked bilateral exophthalmos, in neither was it progressive. The remaining 11 patients had mild, persistent exophthalmos, without other postoperative difficulties.

Six patients experienced recurrence of thyrotoxicosis eight months to four years after operation. In 2 of these cases prolonged treatment with iodine induced permanent remission. Two patients underwent second operations, one experiencing a good result and the other disappearing from the clinic after the operation. There was no record of the courses in the remaining patients with recurrence after the diagnosis was established.

Five additional patients experienced persistence of the disease after operation. Two of these were referred to radiologists for radiation therapy. Two patients with persistent disease could not be followed. The fifth was of special interest in that three operations were performed. At the first, 76 gm of thyroid tissue was removed, a less extensive procedure than was considered optimal being carried out because of the poor state of the patient. Still was observed to have persistence of the disease but for seven years refused further treatment. The

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INFANTILE CORTICAL HYPEROSTOSES*

Report of a Case

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AFFEY and Silverman¹ in July, 1945, published the following description of a new syndrome entitled "infantile cortical hyperostoses"

The principal features of the disorder include onset in the early part of the first year, tender swellings in one or more of these sites — face and jaws, scapular regions and

Scurvy and syphilis were definitely ruled out. Infection, however, was not so satisfactorily excluded. Bacterial infection was not proved in any case. Virus infection or an allergic reaction was considered as a possible cause of the disorder.

Smith et al.² recently published an article relating to a condition occurring in infants and sometimes in older children characterized by irritability, fever, anemia with leukocytosis and a periosteal reaction of various bones. They reported 7 cases in which the most constant observation was a varying degree of periosteal reaction producing new bone and giving a laminated, onion-peel appearance. Biopsies of the affected bones and routine studies were of no aid in ascertaining the etiology of the condition. Biopsies of the affected muscles in 2

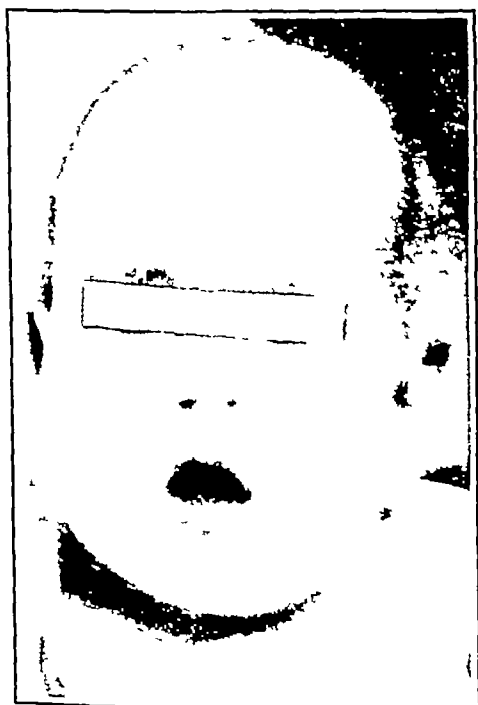


FIGURE 1 Photograph of Patient

Note the typical facies produced by bilateral swelling of the maxilla

extremities, and multiple scattered hyperostoses demonstrated roentgenographically in bones adjacent to the tender swellings and also in several other bones whose overlying soft tissues appear to be normal, clinically and roentgenographically. Biopsies of the affected bones in 3 cases showed only hyperplasia of the lamellar cortical bone.

Fever was noted to have occurred in 3 cases. In 1 case there was hyperirritability, and in 1 a blood count disclosed a moderately severe anemia. In all cases the swelling over the site of involvement tended to progress rapidly and to regress slowly.

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FIGURE 2 Lateral Oblique Projection of the Left Mandible. This film shows the diffuse thickening and the irregular contour of the inferior border.

cases, however, showed evidence of dystrophy suggesting a metabolic factor. Sulfadiazine and a high vitamin C intake did not affect the course of the disease. Penicillin was not tried. All the patients survived, most of the cases clearing completely.

The following case showed clinical manifestations and x-ray findings similar to those reported in the two papers cited above.

A. L., a 3-month-old boy, was admitted to the Charles V. Chapin Hospital on April 24, 1946, with a questionable diag-

few other recurrences of hyperthyroidism may have developed among the small number of patients whose records covered only six months of the post-operative period

Although this is a teaching hospital, thyroid surgery is not done by the house staff until late in the training period. In this connection, it may be noted that the incidence of complications in the hands of the house staff was not appreciably different from that of the visiting staff with one important exception. Three of the 4 deaths occurred after operations by members of the house staff, although this group performed less than half the procedures.

Since the end of the period during which this study was made, changes have taken place in the method of caring for patients with Graves's disease—chiefly in the preoperative use of thiouracil, alone or followed by iodine. This use of thiouracil may result in a lowered mortality because complete control of the metabolic evidences of the disease are made possible. It is apparent, however, that this will not appreciably alter such complications of surgery as hypothyroidism, parathyroprivia, vocal-cord paralysis or the persistence or recurrence of the disease. It may further be mentioned that the preoperative use of thiouracil entails the administration of this drug from three to eight weeks, and it is generally recognized that it is in the first nine weeks of treatment that the serious reactions to thiouracil are likeliest to occur.⁸ Thus, this form of treatment may subject the patients to most of the hazards of medical therapy and subsequently to those of surgery as well. It therefore seems probable that the results of surgery alone, as herewith recorded, approximate those to be expected with the preoperative use of thiouracil.

It is hoped that these figures will help to define the efficacy that medical treatment must achieve if it is to replace surgery in the therapy of Graves's

disease. That such a definition is necessary can readily be demonstrated. Although much has been written about the surgical treatment of this disorder, few authors have described the exact pre-operative status of their patients. Thus, Frazee and Mosser,⁹ describing the end results from the surgical treatment of hyperthyroidism, fail even to mention hypothyroidism, nerve injuries or parathyroprivia. Possibly, this lack of scrutiny was fostered by the absence at that time of a satisfactory alternate method of treatment.

SUMMARY

A review of the records of 149 patients surgically treated for Graves's disease at the Peter Bent Brigham Hospital from 1933 to 1940 showed that satisfactory results were obtained in 113 cases. Persistent or recurrent thyrotoxicosis, lasting parathyroprivic tetany or serious vocal-cord paralysis followed operation in 13 cases, and 4 patients died. The records in 19 cases were incomplete for a minimum of six months following operation.

REFERENCES

1. Astwood E. B. Treatment of hyperthyroidism with thiouracil. *J. A. M. A.* 122:78-81, 1943.
2. Thompson W. O., Morris A. E., and Thompson P. K. Thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter. *Arch. Int. Med.* 46:946-978, 1930.
3. Thompson, W. O. and Preston, F. W. Persistence and recurrence of toxic goiter following subtotal thyroidectomy. *West. J. Surg.* 365, 1941.
4. Fulton, M. N., Schnitker, M. A., and Cutler E. C. Recurrent and persistent thyrotoxicosis following thyroidectomy. *West. J. Surg.* 46:619-627, 1938.
5. Thompson W. O., Taylor S. C. G., III, and Meyer K. A. Factors influencing operative mortality in exophthalmic goiter. *Ann. Int. Med.* 8:350-359, 1934.
6. Macs U., Boyce F. F., and McFetridge E. M. Clinical problems of thyroid disease in non-endemic area. *Am. J. Surg.* 24:232-257, 1934.
7. Clute H. M. Operative mortality in goitre. *New Eng. J. Med.* 206:1240-1243, 1932.
8. Van Winkle, W., Hardy, S. M., Hazel G. R., Hines, D. C., Newcomer H. S., Sharp, E. A., and Sisk W. N. Clinical toxicology of thiouracil survey of 5,745 cases. *J. A. M. A.* 130:343-347, 1946.
9. Frazier C. H. and Mosser W. B. End results from surgical treatment of hyperthyroidism. *J. A. M. A.* 90:657-659, 1928.

erved to be rapidly enlarging. During that time the child took his food fairly well but vomited occasionally. Physical examination disclosed a well developed and well nourished but slightly pale infant. In the right parotid region there was a rather firm, nonred swelling that seemed to be attached to the ramus of the jaw (Fig. 1). Palpation of this area caused the child to cry. The mouth showed no signs of disease.

Examination of the blood revealed a red-cell count of 80,000, with a hemoglobin of 68 per cent, and a white-cell count of 24,000. Nineteen days later the white-cell count was 29,800, with 40 per cent neutrophils, 47 per cent lymphocytes, 9 per cent monocytes, 3 per cent eosinophils and 1 per cent basophils. Examination of the urine showed an occasional granular cast and an occasional white cell per high-

the calvarium external hyperostoses of both parietal bones can be demonstrated in the film of May 7, 1946. In a later film of the thorax, a massive cortical thickening of the right clavicle is seen. The remainder of the skeleton is normal roentgenographically. There are no signs of scurvy, syphilis or rickets.

The patient continued to run an intermittent fever, the temperature going as high as 102.5°F, and continued to be irritable. During his first stay in the hospital, he received a total of 2,400,000 units of penicillin intramuscularly and at another time received 10 gm of sulfadiazine. Neither of these agents altered the course of the disease.

The swelling in the right side of the face continued to enlarge, and about 2 weeks after admission a 4-cm, raised,

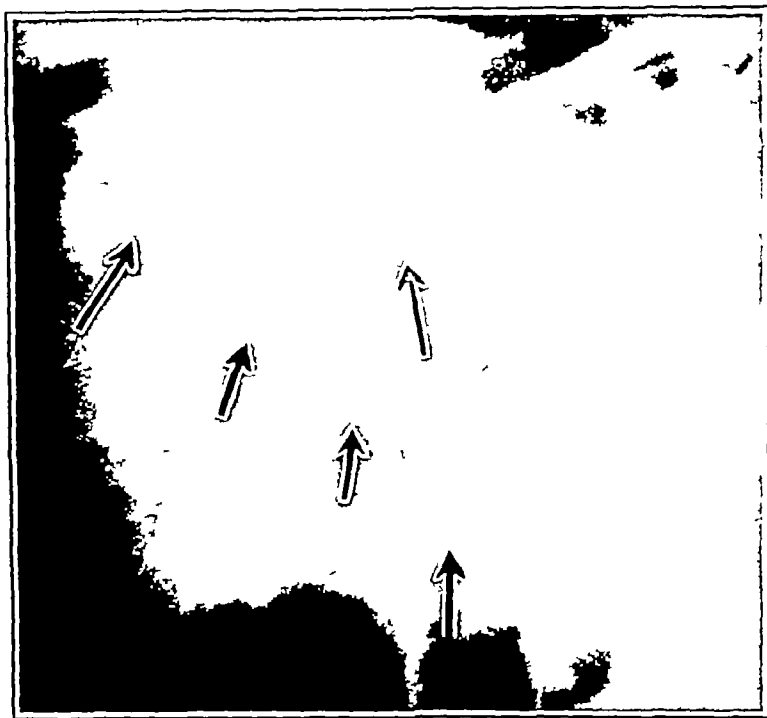


FIGURE 5 Lateral Projection of the Lower Left Ribs

This film shows thickening and broadening of those areas indicated by the arrows

in the sediment on several specimens. Nose and throat cultures were negative for diphtheria bacilli and hemolytic streptococci. The spinal-fluid findings were normal. A blood culture was sterile after 7 days' incubation. Tuberculin and blood Wassermann reactions were negative. The serum calcium was 9.7 mg, and the serum phosphorus 5.4 mg per 100 cc.

X-ray films of the jaws, skull and the entire skeleton were not revealing, and at that time the diagnosis was thought to be mainly confined to a lesion in the parotid gland. The second set of plates, taken about 3 weeks after admission, revealed definite changes in the mandible, the differential diagnosis varied between an infectious process, osteomyelitis and sarcoma.

The diagnosis of infantile cortical hyperostoses was then entertained, and the plates (those taken before May 26) and a copy of the clinical abstract were sent to Dr. John Caffey, who confirmed the diagnosis and interpreted the plates as follows:

Cortical hyperostoses are visualized in several sites of the skeleton. There is a massive mandibular hyperostosis confined to the right side of this bone, which thickens the body, ramus, coronoid process and articular process. In

red area that at first seemed soft appeared in the right occipitoparietal region. This mass was needled, and a culture of the solid material obtained grew out a few colonies of *Staphylococcus albus* and a rare one of *Staphylococcus aureus*. This was followed by the appearance of a similar mass on the left side of the head.

About 1 month after admission, following a transfusion, examination of the blood showed a red-cell count of 4,330,000 with a hemoglobin of 76 per cent and a white-cell count of 18,550. The differential was relatively unchanged. The white-cell count on June 20 was 36,450, with 34 per cent neutrophils, 63 per cent lymphocytes and 3 per cent monocytes.

On May 29, the patient was transferred to the Rhode Island Hospital for further treatment. On the morning of transfer a painful reddish swelling was noted in the region of the right sternoclavicular junction. The following is a detailed x-ray report from the Rhode Island Hospital on films taken on June 8.

Skull The calvarium is not enlarged. In the posterior parietal region and in the posterior portions of the occipital bone, there are several scattered patches of thickening of both the internal and external plates, together with small

nosis of parotitis. The weight at birth had been 8 pounds, 4 ounces, and the birth was stated to have been normal. A slight fever of unknown etiology during the first week of

as were eight siblings. The patient had received no vaccination or immunization. About 10 days before admission, the mother had



FIGURE 3 Anteroposterior Projection of the Jaw
This film shows the thickened areas of bony involvement. The arrows point to the hyperostotic regions of the mandible and clavicles.

life passed away without sequelae. Bottle feedings of an evaporated-milk formula were taken well, and orange juice

that the child was irritable and cried whenever he was touched around the right side of the face. No fever was noted at that



FIGURE 4 Anteroposterior Projection of the Thorax
This film shows the hyperostotic involvement of both clavicles and the anterior and axillary portions of the ribs indicated by arrows.

and cod-liver oil in adequate amounts were started at 1 month of age. The mother and father were living and well,

time. An actual swelling around the right parotid region, noted by the mother about 1 week prior to admission, was

MEDICAL PROGRESS

SYPHILIS

G MARSHALL CRAWFORD, M D *

BOSTON

WITH the termination of World War II and the return of several million young men to civilian life, the program for the control of syphilis faced with a great problem. In spite of the best wartime venereal-disease rates for any nation history, it is exceedingly important that consistent effort be maintained to eradicate syphilis. Even extremely efficient military supervision at separation centers cannot prevent the release of some cases of uncontrolled fresh infection. The cessation of large-scale effort by the armed forces requires increased public-health activity. Plans for the future in this respect, in addition to the continued study of newer methods of therapy, constitute the most significant phases of the problem of syphilis at present.

PUBLIC HEALTH

The most widespread case-finding program ever attempted was introduced by Selective Service before the United States entered the war. Protection of the armed forces from infection was greatly furthered by intensive contact-tracing measures instituted by the United States Public Health Service and local health departments. Most of the burden of this work now falls to civilian health authorities in the face of an increasing number of young men returning to civilian life. A great deal of careful planning for further procedures is required. Lacking the uniformity of military control, the Nation must return to the enforcement of laws and regulations by each community. It has been pointed out that a loose legal framework is now in use in many states for control of the venereal diseases.¹ Existing laws and regulations are for the most part merely adaptations of those designed for the control of other infectious diseases. Since each contagious disease presents unique problems, the application of such laws to any one type of infection cannot be expected to give the best possible results. As the laws stand, the principles of individual civil liberty are not always sufficiently protected. Health departments guarding the public against venereal disease ought not to depend wholly on law-enforcement machinery. Coercive methods should be used only as a last resort in the exceptional patient who is infectious and proves refractory to all methods

of persuasion. It may seem hopeless in some cases to obtain co-operation through persuasion and education, but experienced workers in this field find that it can be done in all except a few cases. When rapport can be established with such a recalcitrant patient, it is usually productive of far greater and more lasting co-operation. Resorting to enforcement of regulations by police officers often results in still greater antagonism.

Incidence of Syphilis

A survey of 5000 military inductees who were suspected of having syphilis showed that 570 (11.4 per cent) were proved to be completely free of the disease.² Most of these cases were included on the basis of a single positive blood test. There was considerable doubt concerning the diagnosis in an additional 6.3 per cent, and another 10.6 per cent were probably cured of the infection. Thus, only slightly more than 70 per cent of the original 5000 suspected cases were shown to have syphilis that required attention. Nearly 60 per cent of the patients in this group had not been treated and had had previously unrecognized infections. This emphasizes the great ease with which syphilis may spread unobserved through the general population and probably through the hands of many practicing physicians. In all, the blood serologic tests for syphilis of the Selective Service disclosed more than 700,000 cases.³

A study of venereal-disease rates in the Army after the termination of fighting in various theaters of operation revealed a sharp rise in the incidence of infections.⁴ These data included both the war areas and the United States itself. The relaxation of military discipline, compulsory educational procedures, provision of prophylaxis and treatment of infected military personnel, as well as the resultant loss of contact information, will sharply increase the burden on civilian health authorities. Although separation centers examined all soldiers for evidence of venereal disease within forty-eight hours of release and treated those with infection, many early cases doubtless slipped through during the stage when a diagnosis was impossible. The United States Public Health Service received reports on all infected soldiers requiring follow-up care and in turn notified the appropriate state health departments regarding the need for further diagnostic

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areas of punctuate decalcification. One of these areas corresponds to the region of soft-tissue prominence in the right side. The soft-tissue prominence on the left side does not correspond to a similar area. No other definite productive or destructive bone lesion is seen elsewhere in the skull. There is no diastasis of the sutures.

Mandible. The entire mandible shows a diffuse general enlargement, with a somewhat lobulated inferior border (Figs 2 and 3). On both sides the limits of the original bony mandible can be distinguished, together with the additional layers of fairly solid bony substance. The outlines are smooth. No destructive areas are visible.

Clavicles. The left clavicle shows a large spindle-shaped mass of bony material surrounding somewhat more than the lateral half of the bone chiefly along the upper surface (Figs 3 and 4). The bony mass is uniform and also shows a slight lobulation in places. No destruction of the original clavicle can be seen. The right clavicle shows a more advanced stage of apparently the same process (Figs 3 and 4). Here, the additional bony accretion is also along the upper surface, where there is likewise a definite, lobulated peripheral outline.

Spine. The cervical, thoracic and lumbar spine shows a normal alignment and no definite productive or destructive bony lesion. There are no definite congenital anomalies.

Ribs. On the left side the 3rd, 4th and 5th ribs show zones of similar bony deposits along the axillary portions (Figs 4 and 5). The inner surfaces of these bones are projected in two areas along the lateral costal wall resembling lines of pleural exudate. Similar appearances are also seen along the anterior portions of the 9th, 10th and 11th ribs on both sides.

Pelvis. No definite bony abnormalities are observed in the pelvic bones. Both hip joints show normal development for the patient's age.

Long bones. The examination includes both humeri and the entire lower extremities on both sides. No definite productive or destructive bony lesion is noted in any of the bones.

Conclusions. The appearances are consistent with those found in a newly described syndrome, which has been called "infantile cortical hyperostoses."

On return to this hospital about 2 weeks later, the clavicles were both enlarged, they were not red but were slightly

tender to palpation. The two swellings on the head had decreased in size but were still firm and slightly red. The swelling on the right side of the head had broken down. The right jaw looked larger, and with a finger inside the baby's mouth and one outside, the bony reaction was palpable between the fingers. On June 22 the left jaw became involved in a process similar to that involving the right on admission. The left half of the mandible was larger than the right.

The clinical features, laboratory data and x-ray findings of this case conformed with the material gleaned from the cases presented by Caffey and Silverman¹ and Smyth et al.² The main features were hyperirritability, fever, leukocytosis and anemia. The x-ray films of the mandible, clavicles and certain ribs showed the typical reaction described by one author as a periosteal reaction² and by another author as hyperostosis of the cortices.¹

This case was unique in the fact that there was involvement of the skull and bones of the calvarium.¹

It is remarkable that these lesions develop so rapidly and regress so slowly, but if this patient follows the clinical course of those in previous cases of this kind, the prognosis is good.

SUMMARY

A case of infantile cortical hyperostoses is presented. Penicillin and sulfadiazine proved to be of no value in the treatment of the patient.

REFERENCES

1. Caffey, J., and Silverman, W. A. Infantile cortical hyperostosis: preliminary report on new syndrome. *Am. J. Roentgenol.* 54:116, 1945.
2. Smyth, F. S., Potter, A., and Silverman, W. Periosteal reaction, fever and irritability in young infants: new syndrome? *Am. J. Dis. Child.* 71:333-350, 1946.
3. Caffey, J. Personal communication.

its who completed proper therapy by the older time methods

The control of commercialized prostitution was fixed somewhat after the termination of wartime measures¹² The United States Public Health Service and the American Social Hygiene Association are exerting every effort to continue this important phase of the control of syphilis Hawaii has had a particularly severe problem in this respect,¹³ and the control of prostitution instituted during World War II resulted not only in a drop in venereal-disease rates but also in fewer sex crimes¹⁴

Mortality Rates

A study of the compilation of data by the Bureau of the Census relating to mortality attributable to syphilis reveals interesting material¹⁵ Since 1939 there has been a steady and appreciable decline in deaths due to syphilis, every region of the country contributing to the lowered rates Even in the South, where the highest incidence occurs, there has been a distinct decrease in mortality The most marked decline in death rates for syphilis is for infants under one year of age The rate in the United States as a whole in 1943 was less than one third that in 1933 The mortality rates for paresis have remained practically stationary in recent years A study of mortality of untreated syphilis in the male Negro indicates that the untreated disease probably reduces the span of life by about 20 per cent.¹⁶ A group of 410 Negroes were followed over a period of twelve years to determine this fact A control series consisted of a comparable age group of 201 uninfected Negroes A large proportion of those who died during the time of observation were examined post mortem The effect of the treatment of acquired syphilis on life expectancy has been estimated by a study of admissions to the University of Virginia Hospital over a twenty-year period,¹⁷ including 2908 patients, among these patients 202 deaths were reported Mortality data for the general population from the Virginia State Department of Health supplied control figures Some patients were followed for as long as twenty years, and the average period of observation was four years All causes of death were included in computing life expectancy It was demonstrated that there were highly significant differences between the life expectancy of patients with syphilis and that of the general population, which in that area is unusually stable so that the fluctuation in statistics caused by transients was at a minimum The syphilitic population under investigation was a treated group, owing to an intensive control program carried out over a long period of years It was demonstrated that the life expectancy among the syphilitic group was reduced from 10 to 12 per cent below that of the general population Since the amount of treatment received by these patients is not specified, no estimate can be made of the amount necessary to

counteract the influence of syphilis on life expectancy A comparison of these figures with the 20 per cent decrease in life expectancy among untreated cases¹⁶ indicates that the antisyphilitic therapy prolongs life Treatment should thus be effective in reducing mortality specifically due to syphilis and in offsetting to some extent the effect of syphilis in reducing life expectancy

Schamberg,¹⁸ in a review of the literature bearing on the statistical prognosis of syphilis as based on governmental mortality reports, clinical studies, death and autopsy findings, and life insurance data during the twentieth century, points out that the available evidence indicates that syphilis adversely influences life expectancy only through the effects of its late manifestations in the central nervous and cardiovascular systems He believes that life-insurance companies may insure, at standard rates, the majority of syphilitic patients applying for insurance with no risk of increased death losses This is at variance with the preceding reports,¹⁵⁻¹⁷ but it serves to emphasize the value of treatment The late crippling effects of visceral syphilis can practically always be prevented by adequate therapy instituted before damage has occurred There is a tendency among many physicians to de-emphasize the benefit of treatment in late asymptomatic syphilis This may be justifiable only if adequate therapy has been given in the past and the patient is properly followed

SEROLOGIC PROBLEMS

The diagnosis of syphilis on the sole basis of serologic tests of the blood is fraught with many hazards It cannot be overemphasized that such a diagnosis in the absence of any other finding should be made with exceeding care A clinical evaluation of the results of serologic tests for syphilis in 8000 consecutive cases in a marine hospital¹⁹ is an example of the difficulties that may be encountered One or more tests performed on admission were positive in 226 cases (2.9 per cent) Among these it was eventually decided that 16.8 per cent of cases had false-positive reactions due to upper respiratory infections, virus pneumonia, malaria, smallpox vaccination, scarlet fever, leprosy, balanitis, diabetes, jaundice, infectious mononucleosis, bone tuberculosis and pulmonary tuberculosis There were only 2 cases in which the so-called "general biologic reaction" was considered to account for a false-positive test Few patients with what were considered to be false-negative reactions were subsequently found to be syphilitic The standard qualitative simplified Kolmer-Wassermann tests were employed throughout, each positive test being repeated at least once The Kahn test is reported to have given a higher incidence of false-positive reactions It was concluded that the use of only one standard test may miss as high as 16 per cent of cases It should be emphasized that doubtful serologic tests for syphilis

procedures or treatment. It was the opinion of military authorities that the educational program represented one of the most important features in the control of venereal disease.⁶ This fact should be recognized by all public-health authorities and carried over into civilian life.

The incidence of syphilis in the United States showed a decrease from 1944 to 1945. Syphilis reported for the first time for the calendar year 1944 in the United States numbered 398,907 cases.⁶ This figure dropped to 335,586 cases reported for the first time in 1945.⁷ This represents a reduction of almost 16 per cent but concerns only the cases of syphilis discovered during that period. The new infections (primary and secondary cases) were found to have occurred in almost identical numbers. This indicates that up to the end of 1945, the incidence of new cases of syphilis in the civilian population had not been influenced by the return of military personnel.

Control Measures

A second report on Alabama's legally required blood-testing program for syphilis on all persons between the ages of fourteen and fifty years is now available.⁸ The ninth county in which universal blood testing has been tried included the first predominantly urban group, this is the most populous county in the state and contains the largest city. The experience gained in mass blood testing in eight previous counties had established basic operating procedures and determined methods for ensuring public respect. The program was carried out by highly trained units designed to carry all publicity and establish primary blood-testing stations, auxiliary laboratories, records and statistics, record and reviewing personnel, physician and telephone follow-up service, personal interview and letter-writing follow-up service, secondary operational centers and a rapid-treatment center. This setup had been found to work with exceptional facility, and during a forty-two day period, 271,775 people were actually blood tested. On the first report, 41,072 persons were shown to have either a doubtful, positive or unsatisfactory serologic test for syphilis, only 32,655 had, by the time of publication, been proved to have syphilis. There were 765 patients with primary and secondary syphilis. This incidence of early syphilis was twelve times that normally reported to the health department during a comparable period. The number of infections brought under treatment could not have been accomplished in years of routine health-department work. Such a program of mass blood testing with follow-up study and immediate treatment, when properly publicized, could not but remove much early syphilis from any community. The cost is relatively low when the testing is done on such a large scale. The full value of these public-health measures is difficult to estimate. It should be pointed out that such a

gain against syphilis could be permanently held only if the program were continued at regular intervals. The repetition of such surveys for the group from fourteen to thirty-five years of age seems especially important. Alabama should receive great credit for the institution of such measures on a state wide basis, and this program may well serve as a model for future efforts by others. A similar campaign has been reported from San Antonio, Texas.⁹ Such measures should at least accomplish extensive health education, and even if that were the most noteworthy achievement, the effort would still be distinctly worth while. The importance of the preliminary publicity and education of the public that precede mass surveys cannot be overemphasized. In San Francisco a well conceived educational and case-finding program has been instituted in the industrial field.¹⁰ Educational efforts were directed toward labor groups, and after education of the union heads, the campaign went well. An appreciation of public-health services was fostered among industrial leaders, and with the confidence of both labor and management, the public-health service was able to function smoothly. This illustrates how special groups can be approached to create public awareness of the health, welfare and moral aspects of venereal-disease control.

The value of contact tracing with all new infections cannot be too heavily stressed. An excellent example of how much early syphilis can thus be tracked down may be seen in the story of a small outbreak of early syphilis in western New York.¹¹ Five patients with early cases divulged the names of 25 persons as contacts, and it was possible to locate 23 of these. Nineteen were found to be infected, and all cases but one were of recent origin. Eight of the infected contacts might have failed to see a physician except for the contact investigation. Prompt reporting by private physicians of all cases and intensive epidemiologic investigation can be expected to bring to treatment many patients with early infectious syphilis who would otherwise go untreated and continue to spread infection. Public health measures are vital, but there is no practicing physician anywhere who cannot contribute valuable assistance by personal effort in contact follow-up procedures.

Hospitals are an aid in case-finding when routine serologic tests for syphilis are performed on every admission. Many thousands of new cases have been discovered by this means, and the procedure should be strongly urged in all hospitals in which such tests are not at present done. Hospitals will play an increasingly important role in the control of syphilis owing to the advent of penicillin. Nearly 100 per cent of all patients with syphilis could complete the required amount of treatment in a short period if institutionalized. This is too great a burden for present hospital facilities but is a worthy goal, in view of the comparatively small percentage of pa-

laboratory studies, it was necessary in most cases to establish the diagnosis on the basis of biologic findings. Elaborate batteries of tests evaluated according to a special classification procedure proved to be the most satisfactory method of studying the material. Many borderline cases are extremely difficult to decide. One might question the possibility that it could become too costly to give treatment in doubtful cases when penicillin therapy is developed to the point of ready facility of application. Another report covers the observation of 300 healthy seronegative reformatory inmates who gave blood donations.²⁶ Almost 100 per cent of these donors developed some degree of positivity, which reverted to negativity in eight weeks. The serums of these patients were subjected to repeated tests for syphilis by six serodiagnostic clinics. A second report from multiple donors observed at the American Red Cross Blood Donor Service²⁷ indicated that there is a tendency for positive serologic reactions to diminish rather than to increase with multiple donations.

Seroresistance

An unusual article by Moore,²⁸ which is worth reading by anyone who treats syphilis, presents a discussion of the problem of seroresistance (so-called "Wassermann fastness") in syphilis, primarily to guide the physician in discussing this matter with his patient. The difficulties encountered in attempting to explain such situations to even the most intelligent person are graphically portrayed, and simple explanatory devices outlined. The reasons for giving treatment even when no physical evidence of syphilis exists and no history of the disease is obtained are shown. The value of yearly physical examinations and semiannual tests of the blood are pointed out. This paper answers many questions that frequently confront both the physician in general practice and the specialist dealing with syphilis.

CLINICAL PROBLEMS

With the bulk of emphasis in current literature dwelling on various phases of penicillin therapy and public-health problems, there have been fewer reports than usual on the everyday clinical problems in the management of syphilis. A few articles nevertheless merit consideration.

Beerman²⁹ has presented an instructive survey of reinoculation of human beings with *Treponema pallidum*. He points out that the introduction of each new curative agent or method of therapy is accompanied by increased reports of reinfection. Beerman believes that part of this may be a reluctance on the part of the supporters of a new therapy to accept the possibility of relapse. After a complete and extensive review of the literature, it is pointed out that reinoculation with *T. pallidum* can be successful in all phases of untreated human syphilis

(superinfection). The reinoculation lesions resemble those representing the phase of the patient's syphilis at the time of reinoculation. Beerman believes that reinoculation of patients supposedly "cured" of syphilis (reinfection) rarely occurs. He does not consider the data on reinoculation of human beings with syphilis sufficient to answer definitely the question whether reinfection is possible in man. Although there may be some justification in the claim that foreshortened treatment schedules prevent the development of immunity, the data available cannot be construed as a rational basis for the voluminous number of cases of reinfection reported in patients treated by intensive therapy. It must be remembered, however, that there are no absolute criteria of biologic cure or adequate means of identifying asymptomatic infections in man, and it is possible that reinfections may take place on a scale larger than hitherto suspected. In this connection, it is interesting to note the report of a chancre developing in a patient with cardiovascular syphilis.⁴⁰ The patient had had adequate therapy for syphilis, and the serologic tests had been negative for several years. The syphilitic cardiovascular disease had apparently been arrested. Such a case presents a nice problem of reinfection versus superinfection.

The occurrence and significance of fever in syphilis have received little attention, since succeeding generations appear to offer milder clinical manifestations of the disease. Wallman⁴¹ has reviewed the significance of fever in syphilis. He points out that it may occur in the secondary phase of the disease and is occasionally observed in early syphilis without eruption, an intermittent fever can occur and may be confused with malaria. A moderate temperature accompanied by generalized muscle pain and gastric disturbance is occasionally found. There are also completely irregular patterns. Hypopyrexia may also occur in either acquired or congenital syphilis. Pyrexial activations during therapy are discussed. Thermal reactions may also be seen when latent syphilis becomes activated, whether spontaneously or by physical trauma, intercurrent disease and so forth. Wallman regards thermal reactions occurring during the treatment of syphilis as an index to the resistance of the *T. pallidum* and believes that in such cases the dosage of drugs should be increased or other measures employed.

Jordon and Dolce⁴² have recently recorded observations in 169 cases of late syphilis over a period of ten years or more. It was found that there is a decided tendency for the blood serum of the patients who were untreated or poorly treated to fluctuate over a period of years. Consequently, the negative serologic reaction in such cases, even on repeated examination, does not necessarily mean spontaneous serologic cure. Approximately 25 per cent of the untreated or poorly treated patients with latent syphilis became seronegative spontaneously and remained so over a period of years. From 20 to

should not be regarded as insignificant any more than they can be used as direct evidence of syphilis. Nor can a negative report be overlooked in the face of clinical evidence. The value of more than one test for syphilis, as well as the employment of different types of reactions, is further emphasized by the fact that some procedures give lower percentages of false-positive reactions under different circumstances.²⁰ The Hinton test, for example, shows a lower incidence of such reactions in malaria. Upper respiratory infections and immunization procedures produce fewer false-positive reactions with the Kolmer type of complement-fixation test. Temporary variations in the seroglobulins may give rise to temporary false-positive tests for syphilis. In the vast majority of cases, false-positive reactions are of low titer and usually disappear within a comparatively short time. The possibility of technical errors must always be kept in mind. The diagnosis of syphilis on the basis of blood serologic tests alone may be so complicated as to require repetition of the tests for weeks or months, as indicated in each case. A rather complete summary of this problem, presented in readable form by Kampmeier,²¹ merits the consideration of anyone faced with such a diagnostic dilemma.

There are continued attempts to refine the techniques and to develop new methods designed to eliminate nonspecificity in the blood serologic tests for syphilis. Kahn²² reports on the use of the so-called "zone reactions" — a serologic method based on the use of multiple serum-antigen ratios that is mainly useful in known or suspected cases of syphilis in which serodiagnostic tests give what are suspected of being false-negative results. Kahn also believes that the procedure provides a better criterion of cure than negative results by standard tests. Rein and Elsberg²³ have published a critical dissertation on the practical value of current verification tests in the serodiagnosis of syphilis. Six methods were considered that have been described for the differentiation of the true-positive from the false-positive serologic reactions for syphilis. It is the opinion of these authors that none of the verification procedures have been able to distinguish consistently between true-positive and false-positive tests. This belief, shared by a number of other serologists, in addition to the impracticability of verification tests in most laboratories, has limited the use of such procedures to large institutions where research facilities are available. Microflocculation tests for syphilis using cardiolipin antigens have recently been described.^{24, 25} It is claimed that a comparison of the test results by these techniques with those by other methods indicates a satisfactory level of sensitivity and specificity. There is some belief that cardiolipin antigens may prove more sensitive than those previously employed. Quantitative serologic tests continue to be used for special diagnostic problems.²⁶ These are also impractical for routine

application because of the larger amount of serum required and the higher degree of technical skill involved. It is possible to follow the serologic trend in various phases of syphilis under treatment with such quantitative tests, which are of great value in estimating the effectiveness of treatment in early syphilis. The application of these principles to various phases of syphilis has recently been discussed.²⁷

False-Positive Reactions

A careful survey was undertaken by the syphilis division of the Johns Hopkins Hospital²⁸ to determine whether positive blood serologic tests for syphilis may be differentiated from reactions due to other factors by means of serologic methods at present available. Serums were obtained from known cases of syphilis, from patients having biologic false-positive tests, from cases of undetermined status, from a normal group and from cows and horses. Specimens were shipped to various laboratories for the performance of numerous serologic tests, including several special techniques. According to this study, there is no "serologic pattern" that will differentiate true from false reactions or one type of syphilitic infection from another. Apparently, no single test or combination of tests was found capable of diagnosing true from false positivity by examination of a single specimen of serum. Until new serologic methods can be developed, differential diagnosis between syphilis and other reagin-producing diseases must continue to be made by clinical examination and by serial quantitative serologic tests repeated over periods of days to years. The frequent warning regarding clinical study of each case²⁹ and attempts to rule out causes for false-positive reactions³⁰ are to be found in practically every article dealing with this problem. Varicella is one of the more recently described possible causes of false-positive serologic tests for syphilis.³¹ Lymphogranuloma venereum has likewise been added to the list.³² The influence of malaria on the serologic tests for syphilis continues to be studied.³³ Apparently, there is no relation between the degree of temperature in malaria patients and the number of false-positive reactions. There is also no apparent correlation between the number of attacks of malaria and the development of positive serologic reactions for syphilis, nor has this disease been proved to produce any change in the spinal fluid.³⁴

The occurrence of false-positive reactions in serologic tests for syphilis following repeated blood donations has received considerable study. Stokes et al.³⁵ reviewed the findings among specimens collected from 210,261 Red Cross blood donors over a nine-month period, 489 of which gave definite positive reactions to serologic tests for syphilis. Of these, 79 subjects were selected for intensive follow-up and evaluation, 40.5 per cent were finally adjudged to have syphilis. After exhaustive clinical

it seems advisable to withhold antisyphilitic therapy until a definite diagnosis can be established

THERAPY

The use of penicillin in the treatment of syphilis is again considered a separate main division in this progress report

Intensive Therapy

Shaffer⁴⁸ has reviewed two groups of patients with early syphilis treated by separate intensive therapy schedules, 210 patients received a fifteen and two-week schedule consisting of thirty injections of Mapharsen and eight injections of bismuth. Reactions necessitated the discontinuance of treatment in 7 cases. A second group of 352 patients was placed on an eight-week schedule that included twenty-four injections of Mapharsen and eight injections of bismuth given concurrently. Discontinuance of treatment was necessary in 8 cases. There were no fatal reactions in either group. Shaffer found that the results of treatment were essentially satisfactory in both series, but only among those who followed treatment faithfully. His opinion is that these intensive plans are satisfactory and adaptable to either private practice or clinics, but that case holding presents the greatest problem. A less satisfactory rate of cure was observed in a group of 206 patients with early syphilis, given two injections of Mapharsen daily for a period of six days by other workers.⁴⁹

Several studies of liver function in early syphilis under intensive arsenotherapy have been reported. In one group the tests employed were the blood prothrombin concentration, the serum bilirubin level, the retention of bromsulfalein and the rate of hippuric acid synthesis.⁵⁰ Among the 22 patients only 3 were found to have normal liver-function tests prior to treatment, suggesting some degree of syphilitic hepatitis. All cases showed impairment of liver function by one or more tests subsequent to the administration of massive doses of arsenical drugs by the five-day intravenous method. The liver function of all patients returned to normal within six months after the arsenotherapy. This indicates that, although hepatic damage results from arsenotherapy, the injury is not permanent nor is it often sufficient to cause clinically recognizable liver disease. Another series of 49 patients receiving five-day therapy were studied with the following liver-function tests: plasma protein, cephalin flocculation, intravenous hippuric acid and sulfobromophthalein.⁵¹ Approximately 35 per cent showed evidence of liver damage prior to treatment, again indicating active hepatitis during the primary and secondary stages of syphilis. There was no evidence of liver damage in any of these cases subsequent to massive arsenotherapy. Approximately 90 per cent of patients with abnormal tests before treatment exhibited the same or improved liver-function tests

following arsenotherapy. These findings suggest that large doses of arsenoxide given within a five-day period do not usually produce detectable liver damage. The disagreement in these two reports^{50, 51} may be partially due to the diversity in liver-function tests employed.

The massive five-day to eight-day intravenous drip arsenotherapy of syphilis appears to be sliding further into disfavor. This method was studied over a period of ten years by numerous groups of investigators but never reached universal application because of the technical difficulties involved and the high incidence of serious and fatal reactions. Multiple-syringe programs for varying periods of days and weeks were in the process of being evaluated at the time of the advent of penicillin. Although these schedules showed great promise and fewer untoward effects, penicillin now bids fair to supplant them all. Combinations of penicillin and chemotherapy, as pointed out below, seem to show the greatest promise.

The use of hyperpyrexia in ocular conditions due to syphilis has recently received attention. One group of 35 cases was treated with specific antisyphilitic chemotherapy in conjunction with the use of the Kettering hypertherm.⁵² Four of 19 cases of syphilitic atrophy of the optic nerve showed improvement, clinical progression of symptoms was arrested in 7, and the remainder continued to progress. Four of 6 cases of acute syphilitic choroiditis were decidedly improved by this treatment. In 6 cases of acute iritis associated with secondary syphilis excellent therapeutic results were obtained. The therapy was also beneficial in the treatment of interstitial keratitis, with marked alleviation of severe pain and photophobia. A report by Bruetsch⁵³ from the Johns Hopkins Hospital concerns 250 patients with syphilitic primary optic atrophy treated with malaria. It is pointed out that the pathological basis of syphilitic optic atrophy is more like the process of dementia paralytica than that of tabes. Malaria therapy inhibits the inflammatory element, and the degeneration of the nerve fibers ceases. Since the inflammatory process usually advances from the periphery toward the interior, enough normal tissue of the central portions of the nerve is left for useful vision. For three years following malaria therapy the slow progression of failure of vision may continue. In patients who react favorably to this treatment, however, the constriction of the visual fields will gradually expand, evidencing capacity for recovery of partially damaged nerve fibers.

It has been found that there is some value in the use of electric shock in the treatment of dementia paralytica.⁵⁴ This should not be considered a treatment of choice, but regarded as an adjuvant method in cases in which hyperpyrexia, penicillin, chemotherapy and combinations of these may fail.

There has been a belief in some quarters that the

25 per cent of these patients (massed racial groups, including Negroes) developed some cardiovascular complication when observations were included over a period in excess of thirteen years. It was apparent that a blood serum that tended to fluctuate in degree of positivity indicated a relatively good clinical outcome, whereas the persistence of strongly positive reactions predicted a poor clinical outcome. As a corollary it was found that in patients with adequately treated latent syphilis there was a decided tendency for the blood serums to fluctuate. Frank, early syphilis did not appear to provide immunity to late complications. Adequate antisyphilitic treatment apparently reduces the hazard of late serious complications to a minimum, even though in patients with latent syphilis there was only a 17 per cent increase in long-term serologic reversals, compared to the 25 per cent spontaneous reversals after little or no treatment. In well treated latent syphilis there was no apparent relation between the state of the blood serum and the development of late complications. Arsenical drugs seemed more efficacious than heavy metals in preventing late complications. Twenty to twenty-nine injections of an arsenical drug were regarded as constituting adequate therapy. This should be combined with alternating courses of a heavy metal. More than this amount did not result in a reduction of complications. Forty to sixty injections, or possibly less, of a heavy metal appeared sufficient when combined with the adequate arsenical therapy. Further administration of heavy metal did not reduce the likelihood of late complications. The findings of these observers warrant more than the usual consideration. It has repeatedly been emphasized that prolonged periods of observation are essential to determine the adequacy of any form of therapy for syphilis or to gather adequate data of almost any sort concerning the disease. This is the first series on record of more than 40 patients followed for ten years or more in whom adequate examinations and repeated serologic tests were done. Such work requires time and is painstaking and tedious, but affords invaluable information.

The early diagnosis of cardiovascular syphilis has been stressed by Dressler.⁴⁵ A study of 1270 cases of proved syphilis resulted in a diagnosis of cardiovascular syphilis in 30.7 per cent. Seventy-eight of these cardiovascular cases were uncomplicated aortitis. These are comparatively high percentages. Of 128 patients with cardiovascular syphilis who recalled the chancre, a diagnosis of uncomplicated aortitis was made in 38 cases within ten years after the acquisition of infection. Dressler, reviewing his methods of study and criteria for the diagnosis of aortitis, believes that careful study enables one to establish the diagnosis earlier than is usually believed, and states that uncomplicated aortitis can be diagnosed clinically in a patient with an aorta of normal size. It has been claimed that

calcification in the ascending aorta is strongly indicative of syphilis.⁴⁶ A comparison of the clinical, roentgenologic and pathological findings in 44 autopsied cases of syphilitic aortitis were compared with those in a group of 62 autopsied cases of severe arteriosclerosis of the aorta. Linear calcifications in the ascending portion of the aorta were present on the roentgenograms in 22.7 per cent of the cases of syphilitic aortitis, whereas only 3.2 per cent of the arteriosclerotic group were found to have calcium deposits visible in the ascending aorta. Calcification in this location was considered to surpass the reliability of negative serologic evidence of syphilis. Such calcification was seldom found as an early sign of syphilitic aortitis, occurring most frequently in the older patients with relatively quiescent cases of syphilis. A description has appeared of 5 patients who developed serious syphilitic lesions of the vascular or cardiovascular organs in early adult life.⁴⁷ Clinical manifestations of syphilitic heart disease appearing in early decades are comparatively rare. The patients in this group varied from five to thirty-one years of age. The duration of infection in 3 of the cases was known to be two, thirteen and fifteen years. Post-mortem examinations were done in 4 cases.

Headaches after lumbar puncture have been studied in a statistical report by Underwood.⁴⁸ Incapacitating attacks occurred in 19 per cent of 500 cases in which punctures were done. Evidence was presented that bed rest following a lumbar puncture does not reduce the incidence of post-puncture reactions. If a severe headache results, however, bed rest for twenty-four to forty-eight hours should be advised. The use of caffeine with sodium benzoate intravenously may be of value in alleviating the discomfort of post-puncture headache if the patient cannot rest. Sedation before the puncture was not found beneficial. Patients presenting emotional reactions to the spinal tap had incapacitating reactions more frequently than calm, quiet persons. As has frequently been observed by others, patients with neurosyphilis had fewer post-puncture attacks than any other group. The problems encountered in the diagnosis of acute syphilitic meningitis were pointed out in a report of 9 cases, 5 of which presented diagnostic difficulties.⁴⁹ In 2 cases the symptoms developed while the patient was receiving treatment with bismuth preparations. Since syphilitic meningitis often improves without treatment and since patients with other types of lymphocytic meningitis may get well coincidentally with antisyphilitic treatment, such therapy cannot be considered a diagnostic test. Other difficulties that may be encountered are the occurrence of false-positive Wassermann reactions in the spinal fluids of patients with nonsyphilitic meningitis and occasionally false-negative reactions in patients with syphilitic meningitis. Unless the patient is critically

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CASE 33071

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Examination in the Out Patient Department showed palpable cervical, axillary and inguinal lymph nodes, but none were considered suitable for biopsy. An x-ray film of the chest revealed a sharply outlined lobulated mass, 9.5 cm. at its widest point, occupying the region of the great vessels opposite the pulmonary conus and obscuring the outline of the aorta. The lymph nodes at the lung roots were slightly enlarged. The trachea was not deformed or displaced. The lung fields were clear. On the basis of these findings, the patient was given 600 r of x-ray therapy to the mediastinum and 500 r to the groin and lumbosacral spine. Following this treatment there was marked clinical improvement. Several months later he began to have pain in the low back and left posterior hip, which disappeared after x-ray therapy (600 r). An x-ray film had shown an area of destruction in the sacrum. Several months later, while the patient was in another city, a biopsy of a cervical lymph node was reported as showing Hodgkin's disease. During the following two years enlarged lymph nodes appeared from time to time in the neck, mediastinum, axilla and groin. These were treated as they appeared by radiation, with rapid subsidence.

Four years before entry the patient complained of generalized itching, particularly on the legs. At that time there were lymph nodes, 1 or 2 cm. in diameter, in the neck and inguinal regions. The spleen extended to the costal margin on inspiration. X-ray examination of the chest was negative, there were no enlarged mediastinal shadows. He was given generalized as well as local radiation, and

received 15 cc. of radioactive phosphorus (equivalent to 0.44 mc.) intravenously. The itching of the skin was benefited by a constant intake of 50 cc. of viosterol (500,000 units of vitamin D) a week. This dosage of viosterol was continued until entry. Two months later the patient complained of pain in the low mid-back and down the thighs. X-ray examination of the lower spine showed areas of increased density in the tenth and twelfth dorsal and the first, second and third lumbar vertebrae. There was also a small soft-tissue mass in the paravertebral space on the left of the tenth dorsal vertebra, and some involvement of the medial portion of the right ilium. Radiation gave symptomatic relief, but the x-ray findings remained unchanged. Three years before entry the appearance of scattered warts on the legs was noticed. Six months later the only complaint was precordial pain occurring after severe exertion. There were fine inspiratory rales at the left apex posteriorly, and a chest film revealed a small, semicircular, soft-tissue mass between the left eighth and ninth ribs near the vertebra. Otherwise, the lungs were clear. After local radiation the symptoms disappeared, and the patient felt well, the weight reaching 174 pounds. A year before admission he had an attack of herpes zoster over the right side of the neck, upper chest and upper shoulder.

Four weeks before entry, the patient began to feel weak, tired and feverish. He lost his appetite and developed an annoying dryness of the mouth and an increasing thirst. He drank about 4 liters of water a day and passed large amounts of light-colored urine, voiding five or six times during the night. Occasionally, he felt an urge to urinate even though the bladder was not distended. He also became constipated, having only one bowel movement in three to five days, despite the taking of cascara and mineral oil. The eyes became sensitive to light and burned, particularly when he was doing close work. On waking in the morning he had some retching, but there had been no actual vomiting. For several days before entry the patient was forced to go to bed because of increasing malaise, weakness and drowsiness. He had vague muscle aches in the legs and diffuse headaches occurring about once a day, increased by motion of the head. The day before entry he had stiffness and aching in the lumbosacral region. While driving to the hospital, the patient found himself "weaving" all over the street and was unable to judge distances, so that several times he collided with the car ahead of him.

Physical examination showed a well nourished patient who appeared both acutely and chronically ill. He was drowsy and dozed off quietly after the examination. The respirations were deeper than normal. There were bilateral, soft, nontender cervical lymph nodes measuring about 1.5 cm. in diameter. The axillary and epitrochlear nodes were not

use of inoculation malaria for the treatment of neurosyphilis presented a hazard to other institutionalized patients. A recent survey of this problem indicates that accidental transmission of therapeutic malaria practically never occurs.⁵⁵

(To be concluded)

REFERENCES

- Gillis E A. Cooperation of health officers and police departments. *J Ven Dis Inform* 27 62-64, 1946
- Zellermayer, J. Syphilis in inductees: analysis of 5 000 cases. *J Ven Dis Inform* 26 194-198, 1945
- Heller, J R, Jr. Venereal disease epidemiology in wartime. *Am J Pub Health* 35 1210-1216, 1945
- Sternberg, T H, and Howard, E B. Current Army venereal disease rates. *J Social Hyg* 31 530-533, 1945
- Larimore, G W, and Sternberg, T H. Does health education prevent venereal disease? Army's experience with 8,000,000 men. *Am J Pub Health* 35 799-804, 1945
- Venereal Disease Division, U S Public Health Service. Personal communication
- Cases of syphilis and gonorrhea reported for first time in states, territories, and possessions for year 1945. *J Ven Dis Inform* 27 112, 1946
- Smith, W H Y, and Denison, G A. Blood testing and treatment program in Jefferson County, Alabama. *J Ven Dis Inform* 27 94-103, 1946
- Robbins L C, and Green W S. Preliminary report on San Antonio blood test campaign. *J Ven Dis Inform* 27 196-199, 1946
- Koch, R A, Arnstein, L, and Painter, A C. San Francisco industrial venereal disease educational and case-finding program. *J Ven Dis Inform* 27 9-19, 1946
- Mattison, B F, and Harris E H. Outbreak of early syphilis in western New York State. *New York State J Med* 45 1105, 1945
- Staff American Social Hygiene Association. War against prostitution must go on: report on current status of commercialized prostitution. *J Social Hyg* 31 500-507, 1945
- Allison S D. Honolulu myth. *J Social Hyg* 32 77-81, 1946
- Laune F F. Fighting "sin in paradise." *J Social Hyg* 32 67-76, 1946
- Usilton L J. Mortality trends for syphilis. *J Ven Dis Inform* 27 47-52, 1946
- Heller, J R, Jr, and Bruyere, P T. Untreated syphilis in male Negro. II. Mortality during 12 years of observation. *J Ven Dis Inform* 27 34-38, 1946
- Smith D C, and Bruyere M C. Effect of treated acquired syphilis on life expectancy. *J Ven Dis Inform* 27 39-46, 1946
- Schamberg I L. Prognosis of syphilis: critical review of clinical, autopsy, and life insurance studies. *Am J Syph Gonorr & Ven Dis* 29 525-550, 1945
- Lubitz J M. Clinical evaluation of serologic tests for syphilis in eight thousand cases. *Illinois M J* 89 20-25, 1946
- Chargin, L, and Rein C R. Reliability of serologic tests for syphilis. *J Mt Sinai Hosp* 12 111-115, 1945
- Kampmeier R H. Serodiagnosis in syphilis. *J Tennessee M A* 38 404-409, 1945
- Kahn R L. Optimal zone reaction in diagnosis and treatment of syphilis. *Arch Dermat & Syph* 53 633-642, 1946
- Rein C R, and Elsbarg E S. Are current verification tests of practical value in serodiagnosis of syphilis? *J Invest Dermat* 6 113-127, 1945
- Rein, C R., and Bossak H N. Cardiolipin antigens in serodiagnosis of syphilis: microflocculation slide test. *Am J Syph Gonorr & Ven Dis* 30 40-46, 1946
- Harris, A., Rosenberg A A, and Riedel L M. Microflocculation test for syphilis using cardiolipin antigen: preliminary report. *J Ven Dis Inform* 27 169-174, 1946
- Kile, R L, and Lund H. Quantitative serological tests in syphilis. *Bull Acad Med (Cleveland)* (No 11) 30 10-24 (November) 1945
- Weiner, A L, and McNamara, M. Practical application of quantitative serologic tests for syphilis. *Ohio State M J* 41 517-520, 1945
- Scott V, Rein C R, Schamberg I L, Moore, J E, and Epler E. Serologic differentiation of syphilitic and false positive sera. *Am J Syph, Gonorr & Ven Dis* 29 505-528, 1945
- Heyman, A. Biologic false positive serologic tests for syphilis. *J M A Georgia* 34 165-167, 1945
- Page S G, Jr, and Heimoff L L. Biologic false positive serologic tests for syphilis: study of 100 cases. *Virginia M Monthly* 153 159, 1946
- Kane L W, and Henneman, P H. False-positive Hinton reaction following chicken pox. *New Eng J Med* 233 407-409, 1945
- Heyman A, and Webb E L. False positive serologic reactions in syphilis in lymphogranuloma venereum. *J Ven Dis Inform* 27 122-126, 1946
- Cox, C B, and Durant, M J. Influence of malaria on Hinton complement fixation (Wassermann) tests for syphilis. *M J Australia* 1 320-325, 1945
- Robinson, H M, Jr., and McKinney W W. Effect of malaria on spinal fluid and blood serologic test for syphilis. *J A M A* 129 667, 1945
- Stokes J H, Boerner F, Hitchens, A P., and Nemer, S. Non-specific reactions in routine blood testing for syphilis. *J A M A* 130 57-60, 1946
- Barnard, R D, Rein, C R, and Dorn C A. False positive serologic tests for syphilis following blood donation. *Am J Syph, Gonorr & Ven Dis* 30 255-263, 1946
- Boynton, M H. Incidence of positive serologic reactions in multiple blood donors. *Am J Syph & Ven Dis* 30 252-254, 1946
- Moore J E. Seroresistance (Wassermann fastness) in syphilis: discussion for patient. *Am J Syph Gonorr & Ven Dis* 29 133, 1946
- Beerman, H. Problem of reinoculation of human beings with *Syphilis pallida*: review of literature. *Am J Syph, Gon & Ven Dis* 30 173-192, 1946
- Thomas, E W, Wexler G, and Shur, M. Report of chancroid developing in patient with cardiovascular syphilis. *Am J Syph, Gonorr & Ven Dis* 29 604-607, 1945
- Wallman J. Notes on significance of fever in syphilis with reference to hypopyrexia. *J Roy Army M Corps* 85 117-122, 1945
- Jordan J W, and Dolce, F A. Latent syphilis: study of one hundred and sixty nine cases observed ten years or more. *Arch Dermat & Syph* 54 1-18, 1946
- Dressler, M. Cardiovascular syphilis: approach to early clinical recognition and early treatment. *Connecticut M J* 9 844-854, 1945
- Jackman J, and Lubert, M. Significance of calcification in ascending aorta as observed roentgenologically. *Am J Roentgenol* 53 431-438, 1945
- Schamberg I L. Syphilitic vascular or cardiovascular disease occurring early in adult life following acquired syphilitic infection. *Am J Syph, Gonorr & Ven Dis* 30 58-69, 1946
- Underwood, L J. Lumbar puncture headache: statistical analysis of five hundred punctures. *Am J Syph, Gonorr & Ven Dis* 30 264-271, 1946
- Heyman, A. Acute syphilitic meningitis: discussion of problems encountered in diagnosis. *Am J M Sc* 209 664-671, 1945
- Shaffer, L W. Intensive arsenotherapy of early syphilis. *Arch Dermat & Syph* 52 147-154, 1945
- Trow, E J, and Dixon H A. Intensive treatment of early syphilis with oxophenarsine hydrochloride by multiple injections. *Arch Dermat & Syph* 52 155-161, 1945
- Hoffman M M, and Katz, F. Studies on liver function. I. Liver function in early syphilis before and during massive arsenotherapy. *Am J Syph Gonorr & Ven Dis* 29 596-603, 1945
- Thomas L J, and Olaneky S. Study of liver function following massive arsenotherapy for syphilis. *Am J Syph, Gonorr & Ven Dis* 30 272-278, 1946
- Knight H C, and Schachat, W S. Hyperpyrexia in treatment of ocular conditions due to syphilis. *Arch Ophth* 35 271-279, 1946
- Bruetach, W L. Malaria therapy in syphilitic primary optic atrophy. *J A M A* 130 14-18, 1946
- Petersen, M C. Electric shock in treatment of demented paralytic. *Proc Staff Meet Mayo Clin* 20 107-112, 1945
- Bruetach, W L. Public health aspect of malaria therapy of neurosyphilis. *Am J Syph, Gonorr & Ven Dis* 29 494-505, 1945

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CASE 33071

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Four years before entry the patient complained of generalized itching, particularly on the legs. At that time there were lymph nodes, 1 or 2 cm. in diameter, in the neck and inguinal regions. The spleen extended to the costal margin on inspiration. X-ray examination of the chest was negative; there were no enlarged mediastinal shadows. He was given generalized as well as local radiation, and

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Physical examination showed a well nourished patient who appeared both acutely and chronically ill. He was drowsy and dozed off quietly after the examination. The respirations were deeper than normal. There were bilateral, soft, nontender cervical lymph nodes measuring about 1.5 cm. in diameter. The axillary and epitrochlear nodes were not

palpable. In the left groin there was a 5-cm., soft, elongated, nontender mass. The heart and lungs were normal. The liver edge was percussed 2 to 3 cm. below the costal margin. There was a hydrocele 9 cm. in diameter on the left side. The extremities were normal except for scattered large warts over the legs. Examination of the cranial nerves was negative. The pupils were normal and reacted well to light and accommodation. The neck was stiff, and the Kernig test was positive bilaterally. The finger-to-nose test was negative. There was no adiadokokinesis, and no muscle weakness. The tendon reflexes were normal. The abdominal reflexes were absent. The plantar response was flexor bilaterally, sensation was normal.

The temperature was 101°F., the pulse 104, and the respirations 24. The blood pressure was 130 systolic, 85 diastolic.

Examination of the blood disclosed a red-cell count of 2,940,000, with a hemoglobin of 10.5 gm., and a white-cell count of 4500, with 86 per cent neutrophils. The total protein was 5.6 gm. per 100 cc., with an albumin-globulin ratio of 1.5. The nonprotein nitrogen was 52 mg., the calcium 12.6 mg., the phosphorus 4.3 mg., the alkaline phosphatase 1.9 mg. and the fasting blood sugar 145 mg. per 100 cc., and the carbon dioxide 30.5 milliequiv. per liter. The prothrombin time was 22 seconds (normal, 14 seconds). The van den Bergh reaction and a cephalin-flocculation test were negative.

The urine was slightly cloudy and straw colored. The specific gravity was 1.005. The sediment contained 8 to 12 white cells and a few granular casts per high-power field. No sugar or albumin was found. A urine culture yielded abundant colonies of *Staphylococcus albus* and alpha-hemolytic streptococcus. The phenolsulfonephthalein test showed 45 per cent excretion in two hours. The urinary calcium excretion was 1290 mg. in twenty-four hours. A stool was brown, liquid and guaiac negative.

A lumbar puncture revealed an initial pressure equivalent to 150 mm. of water, with normal dynamics. The fluid was clear and colorless and did not clot on standing. There were 450 cells per cubic millimeter, of which 80 to 90 per cent were lymphocytes and the remainder polymorphonuclears. The total protein was 58 mg., the sugar 70 mg. and the chloride 111 mg. per 100 cc. The gold-sol curve was 0001122100. Smears of the spinal-fluid and urinary sediment were negative for acid-fast organisms.

During a twenty-four-hour period following the intramuscular ingestion of 1 cc. of pitressin tannate, the fluid intake fell from 4500 cc. to 2750 cc., and the urinary output went from 3500 to 2000 cc.

An x-ray film of the chest showed a milary nodular process throughout both lungs. There was also an area of calcification in the anterior aspect of the right side of the chest close to the sternum. A

skull film showed multiple areas of calcification in the left frontal region.

On the seventh hospital day the patient became disoriented and increasingly drowsy. He developed a coarse tremor of the fingers on extension. A second lumbar puncture revealed an initial pressure equivalent to 240 mm. of water. The fluid had a ground-glass appearance and formed a pellicle on standing. A smear showed one definite acid-fast organism, a subsequent smear on another specimen was negative. The spinal-fluid culture was negative. Slit-lamp examination showed a keratitis similar to that seen in hypercalcemia.

During the fourth week in the hospital the patient began to lose ground rapidly. He had nausea, vomiting and persistent hiccough. On the thirty-third hospital day he became comatose. He developed a right facial palsy, and the left pupil became dilated. The temperature rose to 104.5°F., and the respiratory rate to 45. The patient died on the thirty-fourth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. RICHARD J. CLARK: This patient's illness may be considered to have started with the right lower quadrant pain for which an appendectomy was performed and following which definite signs of debility appeared. We are told in the early portion of the protocol that a biopsy showed Hodgkin's disease. Certainly, all the preliminary evidence of lymph-node enlargement, including para-aortic and mesenteric nodes, evidence of bone involvement, response to radiation and appearance of pruritus are consistent with this reported diagnosis. I shall accept this as a basic working diagnosis in spite of the danger of so doing in these exercises.

We note that the patient was placed on a large dose of vitamin D, — 500,000 units a week, — which he continued over a period of four years. This is a matter to be kept in mind for future consideration. Precordial pain is mentioned only once, and there were no other findings referable to the heart, therefore, I shall dismiss this as evidence of recurring chest tumor. The development of herpes zoster is a frequent occurrence in Hodgkin's disease.

Four weeks prior to entry we are first told of feverishness, which is perhaps surprising. In long-standing Hodgkin's disease the presence of fever would have been expected earlier. This raises the possibility of some complicating infection. Evidence of polyuria then appeared, and I shall discuss this in further detail subsequently. The urgency of urination and increasing constipation raise the possibility of a pelvic mass. Shortly before entry evidence of central-nervous-system involvement — consisting of headache, photophobia, stiffness of the back and unsteadiness — first appeared, and on arrival at the hospital we find objective confirmation in the patient's drowsy and dazed condition.

ologic examination revealed evidence of meningeal involvement without positive evidence of any in the brain proper

Laboratory studies indicated a blood picture compatible with chronic Hodgkin's disease. There was an elevation of the nonprotein nitrogen, an elevated calcium and a normal phosphorus with a low phosphatase. The blood sugar was elevated on the determination given, and yet we are not told of any glycosuria, this raises the bare possibility of involvement of the pancreas by Hodgkin's disease. The urinary calcium increase, as I understand it, is tremendous. The normal value is 150 to 200 in twenty-four hours. There was evidently urinary-tract infection and possibly a decreased renal function, although we could tell more about that if we knew what the fractional phenolsulfonephthalein excretion showed. There was a low urinary specific gravity, but with the polyuria this is not surprising. One may judge from the total picture that there was probably some decrease in the renal function. The spinal fluid showed an increase to 450 cells per cubic millimeter, chiefly lymphocytes, an increase in protein, a normal sugar and only a slightly lowered chloride. These findings certainly give evidence of some type of meningeal involvement. The sugar content was too normal for a bacterial infection. Could this have been a tuberculous meningitis? We know that active tuberculosis does occur in association with Hodgkin's disease. On the other hand, the spinal-fluid findings are against tuberculosis in that the sugar was rather higher than one would expect to see in this condition, and the chloride was not so low as one would anticipate. For these reasons, it is my inclination to say that Hodgkin's involvement of the meninges is likely. We know that this does occur, and I am told that this spinal-fluid picture is compatible with a lymphomatous involvement of the meninges.

The x-ray report of a nodular process throughout the lung is slightly disquieting. Again, the possibility of tuberculosis looms, but lymphoma may produce a diffuse nodular involvement and we have seen cases in which quite definite evidence of previous pulmonary lymphoma cleared under x-ray therapy and I tend to hold to this latter interpretation. In such cases there is evidence of diffuse calcium deposition in various areas of the body. Calcification may occur in scarred areas of treated lymphoma, and this finding is not a strong point for tuberculosis in the case under discussion.

We are given evidence of increasing cerebrospinal pressure and meningeal involvement, with possible involvement of the brain proper. A repeated spinal-fluid examination showed a pellicle on standing, this is always suggestive of tuberculosis, but may occur in any fluid with a high protein content. Finally, our dilemma is climaxed by the report of a single acid-fast organism. If this is true it is

positive evidence of concomitant meningeal tuberculosis.

DR LEWIS K. DAHL: One of the students detected the organism in the smear, and its presence was confirmed by several of the house officers.

DR CLARK: One cannot laugh off a definite acid-fast organism, if it was found. May we see the x-ray films?

DR RICHARD SCHATZKI: The majority of the old films are not here. One film taken about three years ago shows for all practical purposes a normal chest. This chest film, taken when the patient entered the hospital, shows fine miliary nodules of approximately equal size scattered throughout both lung fields and rather homogeneously distributed. We have another film taken a month later, which shows that the lesions had not grown since that time. As a matter of fact they look somewhat smaller, but since the patient was then extremely ill, the films could not be taken in the same fashion. Certainly the lesions have not become larger. The skull shows flecks of calcium, which stereoscopically were thought to be in the inner table or in the dura.

DR CLARK: Does the skull show evidence of general decalcification?

DR SCHATZKI: It does not.

DR CLARK: None of the other bones that are seen show any definite evidence of decalcification?

DR SCHATZKI: No.

DR CLARK: I have committed myself to a primary diagnosis of Hodgkin's disease, to which I shall stick and which I believe will be found diffusely. I shall not take the time to discuss other differential diagnoses in detail. We might for a moment think of the possibility of Boeck's sarcoid. It mimics Hodgkin's disease and involves all the tissues in question, but the lack of any hyperglobulinemia and the general course of the disease make that diagnosis unlikely.

Beyond the basic diagnosis comes the question of several complicating factors. In the first place there was a high blood calcium, and the question arises whether this patient had a concomitant hyperparathyroidism. The chemical findings are rather against it. The elevated blood calcium and the high urinary calcium are consistent, but the presence of a relatively high phosphorus and a low phosphatase militate against this diagnosis, as does the absence of decalcification in the bone. Recently, an increasing number of cases of vitamin D poisoning have been reported, particularly in people taking large doses of vitamin D for arthritis. Symptoms have been described similar to those experienced by this patient — namely, drowsiness, polydipsia, polyuria, dizziness and anorexia in conjunction with high blood and urinary calcium and renal insufficiency. I believe that this patient had some degree of vitamin D intoxication, with renal insufficiency, which may have contributed to the extremely high

urinary calcium output. The destruction of bone in any metastatic neoplasm such as lymphoma, however, could in itself produce a high blood calcium and a high urinary calcium. I believe that a combination of these two factors was at play in this particular case. We might, however, have expected more evidence of decalcification of the bones from vitamin D over this long period than is demonstrated.

Did the patient have diabetes insipidus? The polyuria and the polydipsia were not so extreme as those seen in some cases in which the intake ranges from 8 to 10 liters a day. However, an intake of 4 or 5 liters may be consistent with this diagnosis. The hypercalcemia in itself may have been a cause of the polydipsia and polyuria. On the other hand, the response to pitressin suggests a true diabetes insipidus. Hodgkin's disease has been known to involve the hypophysis and to produce this condition. We also know that basal meningitis in itself may cause symptoms similar to those of diabetes insipidus. We have strong evidence that some process was involving the cranium, and I assume that lymphoma was found in the meninges and in the substance of the brain. I think that this process had involved either the hypothalamic region or the hypophysis. It seems likely that, in the terminal stages, the process broke through from the hypothalamic region into the meninges, and that event may have been the start of the meningeal process.

The question whether there was also a tuberculous process, miliary in nature, with lung involvement, remains open. It is a definite possibility, and if there was a positive acid-fast organism, we must assume that tuberculosis was present. Even though tuberculous meningitis may have been present, I shall hold to a lymphomatous involvement in the central nervous system in addition. The kidneys may well have shown some damage—either lymphomatous or on the basis of calcium deposition with secondary infection. The finding of renal calculi would not be surprising. Various areas of metastatic calcification were doubtless found.

DR DONALD S KING: The interesting thing about the x-ray studies is the marked improvement demonstrated in the film. The patient was much better after a month than at the beginning. Dr Schatzki, have we ever seen that appearance with Hodgkin's disease?

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DR KING: It is interesting to see this change because if the patient had had streptomycin as was suggested we should have ascribed the improvement to the streptomycin.

DR ALLAN M BUTLER: Unless this patient was bedridden, which he may well have been for a while, and suffering atrophy of disuse, which the x-ray films do not indicate, the amount of vitamin D given probably would not have caused any trouble. If such a quantity of vitamin D is administered today it should not be given as viosterol but as one of the concentrated preparations.

DR DAVID G COGAN: I was interested in this patient because of the eye changes. They are readily overlooked unless one searches for them specifically. A slit lamp is not necessary to see the changes. They consist of a deposition of white opacities of the cornea in the palpebral fissure adjacent to the limbus, and in histologic sections they stain like calcium. This patient represents one of seven whom I have seen at the request of Dr Albright, all had a high blood calcium, but none of them had hyperparathyroidism unless uremia was also present. Three of these patients had a high blood calcium associated with sarcoid, and the other four had a high blood calcium associated with hyperparathyroidism as well as uremia. It is an interesting finding in patients with hypercalcemia that is not generally recognized.

CLINICAL DIAGNOSES

Miliary tuberculosis
Tuberculous meningitis
Hodgkin's disease
Vitamin D intoxication

DR CLARK'S DIAGNOSES

Hodgkin's disease, with diffuse involvement, including hypophysis and meninges
Superimposed tuberculous meningitis?
Metastatic calcification
Vitamin D intoxication
Diabetes insipidus

ANATOMICAL DIAGNOSES

Tuberculous meningitis
Miliary tuberculosis of lungs
Tuberculosis of left adrenal gland and thoracic duct
Vitamin D intoxication
Metastatic calcification of kidneys and (?) posterior lobe of pituitary body
(Diabetes insipidus)
Malignant lymphoma, Hodgkin's type, of retroperitoneal lymph nodes

PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY: Autopsy on this patient showed both Hodgkin's disease and tuberculosis, the tuberculosis being much the more prominent of the two. In fact the only grossly obvious Hodgkin's focus that we found was in the retroperitoneal lymph nodes, which were considerably enlarged. The lungs were peppered with miliary tubercles, all

uch were firm and fibrous, with a minimal nt of caseation. It is quite possible that in utual acute stage they were considerably larger at the time of autopsy and that they actually l, as the x-ray films suggest. Examination of rain showed an extensive tuberculous menin- which Dr Kubik will discuss in a moment. y case of miliary tuberculosis one is always inted in the source. Miliary tuberculosis is not imary disease but is secondary to some older, of the disease. A careful search throughout oody seemed to show only one possible source, left adrenal gland, where a caseous tubercle

has frequently been described following excessive dosage of vitamin D.

DR CLARK: Was there anything in the pancreas?

DR MALLORY: No.

DR CHARLES S. KUBIK: In this case there was extensive exudate chiefly over the base of the brain, with numerous small tubercles, which were easily seen with the naked eye and from which the diagnosis of tuberculous meningitis could be made conclusively at autopsy. The more usual finding is only a small amount of basilar exudate, with little exudate anywhere else, and a number of characteristic tubercles. In practically every case there are

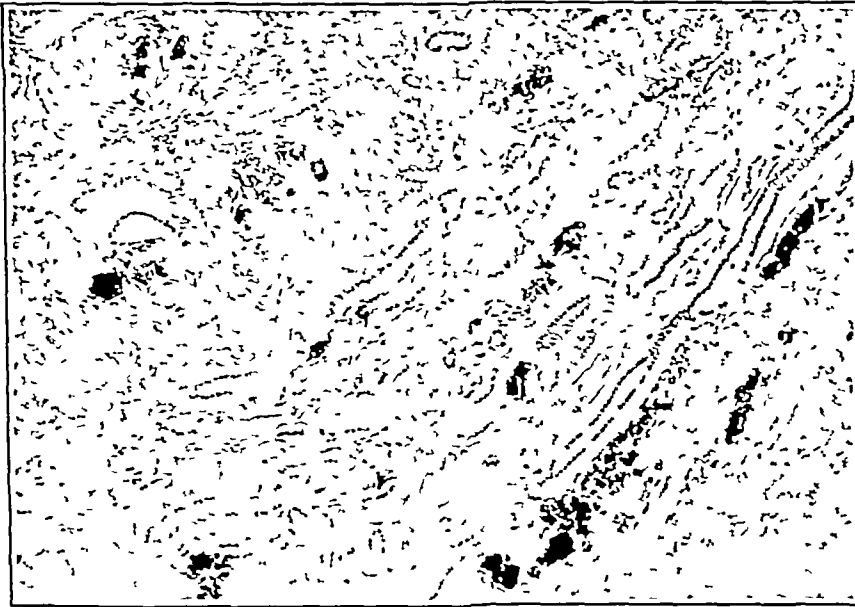


FIGURE 1

omewhat over 1 cm. in diameter was found that was invading a lymphatic vessel in the periadrenal fat. The rest of the tuberculosis seemed to be fresh and acute. The surprise of the autopsy was that the thoracic duct was completely occluded, almost from top to bottom, with caseous material.

The posterior lobe of the pituitary body showed a small lesion, a spicule of dense calcium, one part of which had been slightly organized into bone. This was surrounded by a mass of necrotic polymorphonuclear cells. There was nothing about it to permit a positive diagnosis of tuberculosis. Since calcification was found in other areas there is a possibility that this was a focus of metastatic calcification and not a tuberculous lesion. The kidneys were large, and on gross section innumerable small white specks could be seen, mostly in the pyramids. Sections showed microscopically that these were masses of calcareous material lying close to but always just outside the collecting tubules and occasionally the distal convoluted tubules (Fig 1). The appearance is characteristic of the type of renal calcification that

tubercles of the ependyma of the lateral and third ventricles, particularly the latter. The ventricles are enlarged. On microscopical examination there is likely to be infiltration of the cranial and spinal nerves and, in some cases, of the optic chiasm or tracts. In the case under discussion there was degeneration in one of the third cranial nerves, which probably accounted for the large pupil noted during life. The infection often extends through the arachnoid to the inner surface of the dura and through the pia into the underlying tissues.

CASE 33072

PRESENTATION OF CASE

A forty-eight-year-old married woman entered the hospital because of unexplained fever.

The patient had been well and active until six months before entry, when she began to complain of fatigue. Three months later she developed dyspnea and noticed that she was losing weight. Six

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rtant then to point out some apparent facts. icide was absent, and for this reason the clinical are was not that of obvious intrahepatic infection, such as an infectious hepatitis. One can be that the infectious process did not develop so dly that jaundice did not have time to appear. duration of the fever and of the hepatic enlargement was several months. It is more reasonable to me that an infectious process would have been ociated with focal areas of infection in the form of luple liver abscesses or possibly a single large cess. It is possible that such a spotty type of ction also involved the vascular bed of the liver, h resulting thrombophlebitis. I am sure that intuous hepatitis was not present. Other acute intions, such as brucellosis, do not seem likely, since : clinical course was quite atypical for brucellosis d agglutination reactions were negative. Infec-us mononucleosis could present such a picture, t the blood studies are distinctly against such a agnosis.

What other possibilities are there? One is a new owth, such as a lymphoma of some sort, Hodgkin's ease of the reticulum-cell type or even leukemia. ny one of these may be associated with hepatic largement and with a fever that simulates sepsis. gainst such a diagnosis was the absence of adeopathy and splenic enlargement and the blood findings. Could the hepatic enlargement and fever have een due to metastatic neoplasm, carcinomatous or therwise? There is no evidence of a malignant esion elsewhere. X-ray studies of the gastrointestinal tract were negative, and there were no abnormalities in the urine. There is no clue regarding the possibility of cancer, so far as I can see, with the possible exception of the bloody chest tap.

Could the patient have had cirrhosis of the liver? In such cases fever, pain and an enlarged liver are observed, but the clinical picture presented in the case under discussion was not, to my mind, at all suggestive of this type of hepatic disease. Even in the presence of a superimposed hepatoma, it seems to me that the febrile course was most unusual and probably against such a diagnosis.

If liver abscess is considered, one must mention the possibility of a solitary abscess, conceivably due to amebic infection. Against such a diagnosis was the lack of response to an adequate dose of emetine. In most cases the therapeutic response to this drug is dramatic, and I therefore believe that such a possibility can be ruled out. Furthermore, no cysts or parasites were found in the stools. If multiple liver abscesses caused the septic fever, their possible source must be sought. In most cases the abscesses are secondary to an infectious process related to appendicitis or infection of the biliary tract. We occasionally see hepatic abscesses associated with ulcerative colitis, but this, of course, was obviously not present in the case under discussion.

There could have been a septicemia with metastatic liver abscesses, but four blood cultures were negative. In my experience, it is unusual to have multiple liver abscesses associated with fever of this type without the frequent recurrence of chills. It seems to me that such a possibility should be considered with, let us say, a thrombophlebitis of the portal radicles or even of the intrahepatic veins or of the hepatic vein itself. If such an infection was present, one must again inquire its source. In most cases the process is associated with thrombophlebitis elsewhere, or with focal infection or malignant involvement of the biliary tract with compression of the venous channels in the liver, either hepatic or portal.

The chest findings indicate only a high diaphragm on the right with fluid in the right pleural cavity and with a tremendous enlargement of the liver. I shall not waste time in discussing the x-ray films, unless there is a suggestion of some other findings.

DR JAMES R LINGLEY: That is all they show.

DR JONES: The description of the abdominal films is quite typical of ascites — that is, a ground-glass appearance with more or less obliteration of the soft-tissue outlines. Am I correct?

DR LINGLEY: Yes.

DR JONES: There were ascites and a right hydrothorax. A chest tap showed 670,000 red cells and 18,000 white cells per cubic millimeter, with 80 per cent polymorphonuclear leukocytes. The presence of blood in the pleural fluid may have been due to trauma to a vein but definitely suggests the possibility of cancer or tuberculosis. I have never seen a clinical picture such as this due to tuberculosis. The fluid in the pleural cavity, I believe, could have been associated with a thrombus of a venous radicle in the region of the diaphragm. Most of the trouble was certainly under the diaphragm, and a subphrenic abscess was properly suspected. The patient was tapped in the twelfth interspace and also anteriorly to determine if pus could be located under the diaphragm. So far as the x-ray study is concerned, there could have been a subphrenic abscess with irritation in the pleural cavity above, but such a process does not explain the obvious hepatic enlargement. It is evident that I am groping for an explanation of a mysterious clinical picture.

I have one or two other comments. There is not too much information in the record about liver function, but the fact that the prothrombin time was prolonged suggests that the liver was seriously damaged. There are other factors, such as diarrhea, to explain the prolongation of the prothrombin time. The serum albumin and protein were low. These figures could go with interference with hepatic function and help in part to explain the accumulation of fluid in various parts of the body. They do not have diagnostic significance, however. If straightforward infection had been present in or around the

weeks before entry a physician discovered that she had anemia, the white-cell count was 25,000, with an increase in polymorphonuclear leukocytes. The temperature was normal at that time. Two weeks later she developed night sweats and a temperature swinging up to 105°F. She was admitted to a hospital, where the liver edge was thought to be palpable one fingerbreadth below the costal margin, it was not tender. The red-cell count was 2,800,000, with a hemoglobin of 47 per cent, and the white-cell count 20,000 to 40,000. The sedimentation rate was elevated. A blood culture yielded *Alcaligenes* (type undetermined). The urine showed a + test for albumin, and the sediment contained occasional white cells. There was no urobilinogen. The icteric index was normal. A cephalin-flocculation test gave a + reaction, and the alkaline phosphatase was 5.2 Bodansky units. Agglutination tests for typhoid, brucellar and heterophil antibodies were negative. X-ray films of the chest and of the gastrointestinal tract and a pyelogram were normal, as was an electrocardiogram. Examinations of the stools for amebas were negative. For four weeks before entry the liver increased progressively in size, with occasional bouts of soreness, and the temperature ranged from subnormal to 105°F. During the periods of high temperature the patient was frequently disoriented. With a fluid intake of 2400 to 4000 cc, the urinary output ranged from 300 to 900 cc. Neither 11 gm of sulfadiazine over a forty-eight-hour period nor 3,480,000 units of penicillin administered in two courses of eight days each had any effect on the temperature. An eleven-day course of sodium salicylate, with a total daily dosage of 7 to 60 gm, held the temperature below 102.4°F. This therapy was terminated because of a drop in urinary output. No further reduction in the temperature was obtained with 40 mg of intramuscular emetine hydrochloride given intramuscularly, and the patient grew progressively worse. A week before entry she had slightly icteric scleras and bile in the urine for a day. She also developed slight edema of the ankles and sacrum. Since the onset of the illness, she had lost about 10 pounds in weight.

On admission to this hospital the patient was moderately disoriented, drowsy, dyspneic and dehydrated. The scleras were slightly icteric. There was no palpable lymphadenopathy. The right leaf of the diaphragm was elevated to the inferior angle of the scapula. There were dullness, diminished breath sounds and a few crackling rales over the lower half of the right chest. The heart sounds were rapid and forceful. A Grade II systolic murmur was heard over the precordium. The abdomen was tense and distended. The liver edge was palpable 4 to 5 cm below the costal margin and was extremely tender. The spleen could not be felt. There was no fluid wave or shifting dullness. There was moderate edema over the ankles.

The temperature was 101.5°F, the pulse 110, the respirations 27. The blood pressure was 111/80, systolic, 68 diastolic.

Examination of the blood showed a hemoglobin of 10.6 gm and a white-cell count of 20,600, with 65 per cent neutrophils. The nonprotein nitrogen was 18 mg, and the serum protein 5.7 gm per 100 cc, with an albumin globulin ratio of 1.17, the cholestrol was 92 milliequiv per liter. The prothrombin time was 39 seconds (normal, 19 to 21 seconds), the serum van den Bergh and the blood Hinton reaction were negative, as were four blood cultures. The urine was normal except for a + test for albumin.

X-ray examination revealed a high diaphragm on the right, obscured by increased density in the lower lung field. There was also evidence of fluid extending upward along the lateral chest wall. Beneath the right half of the diaphragm there was a ground-glass density extending down to the right lower quadrant of the abdomen. The right lobe of the liver appeared to reach almost to the iliac crest. The soft-tissue outlines of the entire abdomen were partly obliterated by increased density. No gas was seen in or about the area of the liver. There was no evidence of dilated loops of bowel.

On the third hospital day the right side of the chest was aspirated high in the axilla, and 50 cc of blood fluid containing 670,000 red cells and 12,800 white cells per cubic millimeter was obtained, 80 per cent of the white cells were polymorphonuclear. Aspirations under the twelfth rib posteriorly and under the costal margin anteriorly were negative.

On the fifth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR CHESTER M. JONES. It is obvious that since this patient was operated on she was thought to have a surgical condition that was remediable. I do not believe that she was operated on solely for diagnosis. The history that she presented was one of gradual weakness and a spiking temperature that slowly increased in severity, but she had no chills at any time. The liver enlarged rather rapidly and was tender, but there was no associated jaundice. During the course of the disease, fluid developed in various parts of the body, with edema of the extremities, hydrothorax and probably ascites. There was a considerable leukocytosis, the white-cell count varying from 20,000 to 40,000 cells, always with 80 per cent neutrophils. There were no comments regarding either the presence of toxic granules or any abnormality in the type of white cells seen.

With a spiking temperature such as that noted in this case, the question must always be raised concerning the underlying mechanism. If infection, what type of infectious process could it have been? If not infection, what other process could have given such a persistent elevation of temperature? It is

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

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THE ALCOHOLIC PATIENT

EVER since man first observed the phenomenon of fermentation and noted the effect of its products on the human body, he has been faced with the problem of alcoholism. Only in recent years, however, and still far from fully, has the victim of alcohol, like the sufferer from mental disease, been considered as an ill person.

The consumption of strong drink is again on the increase, and with it we are undergoing a resurgence—we hope a more intelligent one than ever before—in our concern for the drunkard. Contributing to knowledge of the subject is the report issued in 1945 by the special commission appointed by the Legislature to investigate the problem of alcoholism in Massachusetts.

There are now, it is estimated, some 20,000 alcohol addicts in the Commonwealth, and alcohol is largely responsible, in one way or another, for the commitment of 25 per cent of the population of our mental hospitals, in addition, alcoholism is responsible for 26 per cent of the cases handled by the Boston Council of Social Agencies. Alexander, Moore and Leary* found on an analysis of all deaths due to toxic substances from 1928 to 1937 that ethyl alcohol was the cause in 52 per cent.

Eighty out of every hundred prisoners in the Charles Street Jail, according to a recent report, are under arrest for drunkenness, and His Honor, Mayor James M. Curley, has made the sagacious suggestion that the jail be converted into a hospital for alcoholic patients, the cost of its maintenance to be met by increasing the license fee for the sale of alcoholic beverages by \$500 annually.

The proposition that those who profit by the sale of liquor be made at least partly responsible for the cost of its by-effects seems fair. It recognizes also the thesis that alcoholism is a medical rather than a penologic problem. As evidence that an enlightened view of alcoholism is not universal comes a statement from the Massachusetts Commissioner of Probation and others urging repeal of the statute allowing persons arrested for drunkenness to be released without punishment for the first four offenses. With alcoholism considered as a disease, the word "punishment" is objectionable.

The Charles Street Jail, obviously, is scarcely a suitable building for a hospital, nor is it yet clearly demonstrated that more in-patient facilities are required for alcohol addicts. If such a need can be demonstrated, the recently proposed program calling for the utilization of the Bridgewater State Farm is more to the point and deserves careful scrutiny. There is no question that more clinic facilities of one sort or another are necessary.

What is definitely in order is a recognition of the facts, by the medical profession, as well as by others, that alcoholism is a disease, that, as with other diseases, its prevention is more effective than its cure and that the place of the physician is with the various agencies that are striving toward that end.

*Alexander, L., Moore, M., and Leary, T. Deaths from poisoning—incidence in Massachusetts. *J. Crim. Psychopathology* 3:100-111, 1941.

liver, one would expect marked toxic granulation in the white cells. No such observation was made. I believe that it is possible, therefore, to veer away from focal infection in the liver but not from infection adjacent to the liver. I have already suggested the possibility of thrombophlebitis, and I think that there were areas of thrombophlebitis in the portal circuit, in the body of the liver itself or in the hepatic veins at the entrance of the vena cava. I have a suspicion that something like Chiari's syndrome may have been present. This curious clinical picture is always secondary to another process — sometimes an infection and sometimes a metastatic neoplasm infiltrating the liver and compressing the venous channels. I am inclined to doubt a really diffuse infiltrating cancer in the liver because of the complete absence of jaundice. I am more inclined to think that there may have been a malignant process outside the liver. At a guess, I suggest that it might have been a lymphomatous type of neoplasm. I do not believe that there was a single hepatic abscess or multiple hepatic abscesses or that operation was performed with the expectation of finding focal sepsis in the liver. The failure to obtain a therapeutic response from penicillin in no way rules out intrahepatic infection, because undrained sepsis in the liver will not respond satisfactorily to antibiotics.

So far as I am concerned, the absence of chills makes me believe that a primary infectious process in the liver was not present. Pylephlebitis, of course, is a possibility, but I cannot imagine what the initial cause was.

Finally, therefore, I lean to the possibility of some neoplastic disease around the liver, causing its rapid enlargement and fever but little serious interference with liver function. I shall leave it there, but merely add that I believe that what was found at operation was not amenable to surgery.

DR WADE VOLWILER: I was asked to see this patient to consider the possibility of doing a blunt-needle biopsy of the liver to make a histologic diagnosis. The patient was extremely ill, disoriented and delirious and looked as if she would die at any moment. It seemed, in spite of the absence of chills, that focal infection within the liver was entirely possible and that therefore one would not want to do any procedure that might spread sepsis. Also, the prothrombin time was prolonged, and such a procedure would not be safe without a transfusion.

We went for the argument in favor of infection — hook, line and sinker.

DR BEVERLY T. TOWERY: Is not the absence of jaundice against Chiari's syndrome?

DR JONES: No, Kelsey and Comfort* have reported 20 cases in only a small number of which jaundice was present. The syndrome can occur perfectly well without jaundice.

CLINICAL DIAGNOSIS

Liver abscess?

Subphrenic abscess?

DR JONES'S DIAGNOSIS

Neoplastic disease around liver, with intrahepatic thrombophlebitis.

ANATOMICAL DIAGNOSIS

Metastatic epidermoid carcinoma of liver, primary source undetermined

PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY: I do not know whether the Pathology Department is able to explain this case completely. We can, however, state the major diagnosis. The patient was operated on, as Dr Jones suspected, in the hope that a subdiaphragmatic or liver abscess would be found. For the reason the exploration was done posteriorly, the surgeon came down on the superior surface of the liver, which was studded with tumor masses of metastatic carcinoma. A biopsy was performed. The tumor was highly undifferentiated, but I believe that it was an epidermoid carcinoma. This histologic structure was quite consistent with a bronchiogenic carcinoma, but the patient left the hospital without our ascertaining the primary focus.

DR JONES: Do you agree that there might have been enough infiltration into the hepatic substance or around it to produce a partial venous block, thus causing many of the symptoms noted?

DR MALLORY: That is possible but unusual for metastatic carcinoma. In primary liver-cell carcinoma, venous invasion is frequent, and there is reason why it could not occur with metastatic disease.

DR JONES: If I remember correctly this is just what happened in several cases of metastatic carcinoma reported by Kelsey and Comfort.

*Kelsey M. P. and Comfort M. W. Occlusion of hepatic veins in review of twenty cases. *Arch. Int. Med.* 75: 175-183, 1945.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

REPORTABLE DISEASES IN MASSACHUSETTS FOR DECEMBER, 1946

RÉSUMÉ

DISEASES	DECEMBER 1946	DECEMBER 1945	SEVEN YEAR MEDIAN
diphtheria	0	2	*
pox	1331	900	1511
scarlet fever	88	21	20
measles	556	409	517
rubella	4	12	12
typhoid	68	61	68
typhus	316	467	35
gonorrhea	0	0	*
granuloma venereum	0	0	*
syphilis	7	83	4
meningococcal	842	702	1082
Pfeiffer bacillus	9	12	12
pneumococcal	8	2	2
staphylococcal	7	3	61
streptococcal	0	1	01
other forms	0	0	01
undetermined	0	1	21
lobar pneumonia	319	669	670
elutis	114	165	327
influenza	18	11	7
ever	10	5	5
pneumonia	663	523	978
other forms	238	459	433
fever	223	164	239
not fever	16	10	18
cough	2	2	2
reportable December 1945	730	598	598
7 year average.			

COMMENT

Diphtheria was at the highest prevalence for the month of 1935, the number of cases being more than four times the number recorded in December, 1945. Nearly 60 per cent of cases were reported from Boston. Diphtheria tuberculosis was at the highest level since 1942, well below the median for the past seven years. The late seasonal peak kept poliomyelitis above both the average for December, 1945, and the median for the seven-year period. Chicken pox, scarlet fever and whooping cough are just beginning to show trends toward higher levels. Only whooping cough, however, has risen above the median. There has been a decline in the reporting of gonorrhea and syphilis, the former reaching the lowest level since 1942 and attaining the lowest since 1929. Acillary dysentery, measles and mumps were at low levels in the month.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anthrax was reported from Peabody, 1, total, 1. Diphtheria was reported from Boston, 51, Bridgewater, Brockton, 5, Greenfield, 2, Leominster, 2, Lowell, 3, Northampton, 1, Methuen, 1, New Bedford, 4, Palmer, 7, Salem, 1, Somerville, 5, Tewksbury, 2, Wakefield, 1, Waltham, 1, Worcester, 1, total, 88. Dysentery, bacillary, was reported from Newton, 1, Northampton, 1, Springfield, 1, Wrentham, 1, total, 4. Lymphocytic choriomeningitis was reported from Cambridge, 1, Medford, 1, total, 2. Malaria was reported from Braintree, 1, Fall River, 1, East Barrington, 1, Greenfield, 1, Murphy General Hospital, 1, Somerville, 1, Worcester, 1, total, 7. Meningitis, meningococcal, was reported from Boston, 3, Foxboro, 1, Easton, 1, Fall River, 2, Leominster, 1, Waltham, 1, total, 9. Meningitis, Pfeiffer-bacillus, was reported from Boston, 2, Northampton, 1, New Bedford, 2, Rehoboth, 1, Worcester, 2, total, 8. Meningitis, pneumococcal, was reported from Boston, 1, Northampton, 1, Cohasset, 1, Foxboro, 1, Northampton, 1, Worcester, 2, total, 7. Meningitis, undetermined, was reported from Medford, 1, North Adams, 1, total, 2.

Poliomyelitis was reported from Ashburnham, 1, Athol, 1, Boston, 1, Blackstone, 1, Brookline, 2, Fall River, 2, Fitchburg, 1, Framingham, 1, Groveland, 1, Montague, 1, New Bedford, 3, Newton, 1, Taunton, 1, Wellesley, 1, total 18.

Salmonella infections were reported from Boston, 2, Chelsea, 2, Haverhill, 2, Lowell, 2, Melrose, 2, total, 10.

Septic sore throat was reported from Amesbury, 14, Arlington, 1, Boston, 14, Lawrence, 1, Mansfield, 1, Merrimack, 5, Salem, 1, Williamstown, 1, total, 38.

Trichinosis was reported from Cambridge, 1, Falmouth, 1, Framingham, 1, total, 3.

Tularemia was reported from Boston, 1, Tisbury, 1, total 2.

Typhoid fever was reported from Leominster, 1, Marblehead, 1, Salem, 1, total, 3.

Undulant fever was reported from Uxbridge, 1, Wellesley, 1, total, 2.

CORRESPONDENCE

PENICILLIN TREATMENT OF SYPHILIS

To the Editor: Relative to the excellent and timely editorial "Syphilis and Penicillin" which appeared in the December 26 issue of the *Journal*, I should like to call attention to certain parts of it that are at variance with the instructions for the use of penicillin in the state co-operating venereal disease clinics, which are as follows:

All patients with early infectious syphilis (primary, secondary and infectious relapses) and pregnant women with syphilis should be treated with 40,000 units of penicillin given intramuscularly every three hours, night and day, for seven and a half days or until a total of 2,400,000 units has been received, with 0.2 gm. bismuth subsalicylate (1.5 cc. Stabisol) on the first, third, fifth, seventh and ninth days. A Herxheimer reaction, with malaise and fever a few hours after onset of treatment, is to be expected in the majority of cases, but a generalized reaction of this nature is no reason to discontinue treatment.

Serologic and clinical follow-up should be done at the termination of treatment, every month for the first six months and quarterly thereafter until the end of the first year. If the serologic and clinical follow-up is negative the patient should be discharged and advised to return once a year for check-up for the next five years.

In penicillin-treated cases of syphilis in which the periodic serologic and clinical follow-up indicates a relapse the patient should be treated with 4,800,000 units of penicillin, given in 80,000-unit doses intramuscularly every three hours, night and day, for seven and a half days, with 0.2 gm. bismuth subsalicylate (1.5 cc. Stabisol) on the first, third, fifth, seventh and ninth days, unless contraindicated.

In cases in which periodic serologic and clinical examination gives evidence of resistance after the termination of the second course of penicillin, the patient should be referred to the Division of Venereal Diseases, Department of Public Health, for consultation as to further treatment.

All patients with late syphilis are being treated on a consultative basis, the consultation forms being reviewed by Dr. Solomon and his group at the Boston Psychopathic Hospital. This service is available to the private practitioner as well as to the co-operating clinics, and a request to this department should be made for further information on the same. This method of handling the treatment of patients with late syphilis is extremely valuable not only to the patient but also to the physician. Incidentally, there is available to co-operating clinics as well as to private practitioners consultative information for infants and children who are infected with or suspected of having syphilis. Further information may be had by applying to this department.

This information is presented so that private practitioners and possibly the chiefs of the co-operating clinics who receive the *Journal* will not be confused.

VLADE A. GETTING
Commissioner

Massachusetts Department of Public Health
State House
Boston

RETIREMENT PROGRAM FOR HOSPITAL EMPLOYEES

IN THESE days when nonprofit hospitals throughout the country are faced with varied difficulties in obtaining suitable employees, any constructive plan that has for its object the improvement of working conditions for these workers deserves serious consideration. Recently, Mr. John H. Hayes, president-elect of the American Hospital Association and chairman of its Pension Committee, has announced a retirement program for employees in nonprofit hospitals. He points out that hospital workers are not now covered by benefits of the Social Security Act and that this is one reason why hospitals are at a disadvantage in maintaining a high grade of personnel. In the preliminary studies of the American Hospital Association, it was found necessary to establish a plan that could be easily fitted in with Social Security payments when and if the federal laws were changed to include workers in hospitals. It was also kept in mind that the contributions should be on a modest basis to fill the needs of both small and large hospitals and that provision should be made for transferring benefits from one hospital to another.

The final plan was developed in co-operation with the National Health and Welfare Retirement Association. It provides for joint employee and employer contributions, the optional provision by the hospital of benefits for past service, fully vested rights for retirement purposes to the employer's contributions and transferability between hospitals that are members of the plan. In case of death the employee's contributions plus interest are paid to his beneficiary. All permanent employees over twenty-five years of age, with one year or more of service, are eligible to join provided that the hospital votes to make the payments on a payroll-deduction basis.

The National Health and Welfare Retirement Association is a nonprofit corporation organized by community chests and various national welfare organizations and licensed under the insurance laws of the State of New York. Mr. Gerard Swope is chairman of the Board of Trustees, which is composed of sixty representatives from all parts of the

country, including all the members of the Pension Committee of the American Hospital Association. The association started operations on October 1, 1945, and employer-employee contributions already being received at the annual rate of \$2,000,000.

It is believed that this scheme may well be a useful step in re-establishing better relations between hospital employees and employers. It should be of assistance in attracting a better class of workers to fill these much needed positions.

MASSACHUSETTS MEDICAL SOCIETY BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups, such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of dates can be avoided.

DEATHS

HARE — Charles H. Hare, M.D., of Boston, died January 21. He was in his eighty-fifth year.

Dr. Hare received his degree from Harvard Medical School in 1889. He became interested in gynecology and limited his practice to that specialty, having retired more than a decade ago. He was a member of the Boston Obstetrical Society and a fellow of the American College of Surgeons and the American Medical Association. During his period of active practice he had been a member of the staffs of the First Hospital for Women, Massachusetts Women's Hospital, Elizabeth's Hospital, Boston Dispensary, Carney Hospital and Quincy City Hospital.

PHILLIPS — Wilson F. Phillips, M.D., of Dorchester, died January 29. He was in his seventy-fifth year. Dr. Phillips received his degree from Boston University School of Medicine in 1898. He was a fellow of the American Medical Association. His widow survives.

SHEFFERD — Jeannette M. Shefferd, M.D., of River, died October 25. Dr. Shefferd received her degree from Creighton University School of Medicine, Omaha, Nebraska, in 1912. She was a member of the New England Otological and Laryngological Society and a fellow of the American Medical Association.

TILDEN — Irving N. Tilden, M.D., of Massachusetts, died November 3, 1946. He was in his seventy-sixth year. Dr. Tilden received his degree from Harvard Medical School in 1899. He was a former councilor of the Massachusetts Medical Society and was a fellow of the American Medical Association. His widow and a son, Dr. Benjamin R. Tilden, of Massachusetts, survive.

ator Prosthesis Anatomic and physiologic considerations principles of alignment and fitting designed for the arm and limb manufacturer By Atha Thomas, M D, and R C. Haddan 8°, cloth, 305 pp, with 207 illustrations Philadelphia J B Lippincott Company, 1945 \$8 00

ld War II, like all wars, produced a revival of interest in prostheses. More than 15,000 members of the armed forces of the United States lost an arm or a leg. But it is not generally appreciated that forty thousand amputations, requiring prostheses, are carried out in this country every year. In the services the liaison among

cluding a discussion of the use of Tridione. The book should prove of value to all persons coming into contact with sufferers of epilepsy and migraine.

How A Baby Grows A story in pictures By Arnold Gesell, M D, director, Clinic of Child Development, Yale University 4°, cloth, 80 pp, with over 800 photographs arranged and interpreted with the assistance of Katherine G. Walden, A.B. New York and London Harper and Brothers, 1945 \$2 00

This new type of book consists of an atlas, with a simple, explanatory text, tracing the changes in a child's develop-

The Journal lacks extra copies of the February 21, October 3 and November 14, 1946, issues. If any subscribers who do not bind their copies have the above-mentioned issues on hand, the Journal will gladly pay 15 cents for each copy left at or mailed to its office (8 Fenway, Boston 15).

geon, physical therapist and limb fitter is close and efficient, in civil practice it is not infrequently casual and ineffective. This book, written jointly by a well known surgeon and by the president of the Association of Limb Manufacturers of America, should go far toward bridging this gap. It fills a long felt need in presenting in one profusely illustrated and well written volume the essentials of modern management of amputations. The extensive British experience at Roehampton between the two wars is freely drawn on, and an excellent bibliography is appended to each chapter.

n the Doctor's Office The art of the medical assistant By Esther J. Parsons Illustrations by Jean McConnell 12°, cloth, 300 pp., with illustrations Philadelphia J B Lippincott Company, 1945 \$2 00

This manual, which was written primarily for the physician's assistant, the receptionist, secretary, nurse and laboratory technician, discusses in detail her relations with the physician and his patients. The important subjects of handling patients in the office and the conduct of telephonic service are considered frankly, as well as the personality, character and health of the assistants. The care of office equipment, the keeping of records, office bookkeeping and correspondence are discussed. An important chapter on emergency care in the absence of the physician is included. The material is well organized, and the text well written in an easy style. The type is large and printed on a good soft paper, easy to read and to handle. This manual should prove profitable to both physicians and assistants.

ment during the first five years of life. The pictures are arranged to show instantly and vividly how the infant grows from day to day and month to month and why he acts as he does. Part one shows how the baby gains control of his body, and part two portrays the growth of his mental abilities and personality. The pictures, which are based on the average trends of development, do not portray individual variations.

Trauma of the Central Nervous System Proceedings of the Association for Research in Nervous and Mental Disease, December 17 and 18, 1943, New York 8°, cloth, 679 pp, with 243 illustrations and 44 tables. Research Publications, Volume XXIV Baltimore The Williams and Wilkins Company, 1945 \$8 00

This volume contains twenty-seven papers concerning trauma of the head and brain. The first paper, by Dr. Fred A. Metler, is a history of cranial trauma from the earliest times to the nineteenth century. The other papers are devoted to the physiology, histology, pathology, diagnosis and aftereffects of head injuries. This volume should be in all medical libraries and should prove of value to surgeons interested in brain surgery.

New Drugs By Arthur D. Herrick With a foreword by Austin E. Smith, M.D., secretary, Council on Pharmacy and Chemistry, American Medical Association 8°, cloth, 303 pp. New York Revere Publishing Company, 1946 \$4 00

The title of this new book is misleading, since it does not list and consider new drugs but concerns the regulation of new drugs under federal and municipal control. The first part of the book consists of a thorough analysis of the federal Food and Cosmetic Act of 1938 as it relates to drugs and discusses thoroughly the testing of new drugs for the purpose of determining their safety. The various legal procedures relating to the act are briefly outlined.

An appendix of four parts includes a report of the Secretary of Agriculture on deaths due to elixir sulfanilamide. This report was made in response to Senate Resolution 1944 of November 16, 1937, and was published as Senate Document No. 124, 75th Congress, 2nd Session. During September and October, 1937, at least seventy-three persons died as a direct result of taking the elixir. Twenty other persons died, but the exclusive responsibility of the drug was not established. The ninety-three deaths occurred in fifteen states reaching from Virginia to California. Two hundred and forty gallons were manufactured in Tennessee, and owing to the diligence and quick action of the Food Drug Administration the entire amount of unused elixir was retrieved, and this serious

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Science and Seizures New light on epilepsy and migraine By William G. Lennox, M.D., Sc.D. (hon.), assistant professor of neurology, Harvard Medical School, and visiting neurologist, Boston City Hospital. Second edition 12°, cloth, 258 pp., with 10 illustrations. New York Harper and Brothers, 1946 \$2 00

The first edition of this popular book on epilepsy was published in 1941, and since that time it has been found necessary to make seven reprintings. In this second edition, the section dealing with medication has been rewritten, in-

BOOK REVIEWS

Pediatric X-Ray Diagnosis. A textbook for students and practitioners of pediatrics, surgery and radiology. By John Caffey, M.D. 4th ed., cloth, 838 pp., with 710 illustrations. Chicago: The Year Book Publishers, Incorporated, 1945. \$12.50.

The publication of Caffey's volume fulfills a need of long standing for a text and reference for both pediatrician and radiologist. The volume, based on twenty years' experience at the Babies' Hospital, is divided into the following six sections: "The Head and Neck," "The Thorax," "The Abdomen and Gastro-Intestinal Tract," "The Pelvis and Genito-Urinary Tract," "The Extremities" and "The Vertebral Column." Each section opens with a description of the normal roentgenologic appearance, and this is one of the valuable features of the book. The description of the various pathologic processes is thorough, although there are some rather important omissions, and the text is lucid and eminently readable. The reproductions and drawings, which are used freely, are excellent. The general format is satisfactory, and the bibliography adequate.

This book is recommended without hesitation for the library of every radiologist and pediatrician.

Large Scale Rorschach Techniques. A manual for the group Rorschach and multiple choice test. By M. R. Harrower-Erickson, Ph.D., and M. E. Steiner, M.A. 8th ed., cloth, 418 pp., with 157 tables. Springfield, Illinois: Charles C. Thomas, 1945. \$8.50.

The Rorschach (ink-blot) test for mental rating in its group application, originally designed for the military purposes of selection, classification and rehabilitation of personnel, is discussed in detail in this volume. The first part comprises a brief history of the development of the group procedure, its uses and its technical administration. The second is devoted to an experimental investigation on 340 subjects, providing 8526 responses. The results are presented in both graphic and tabular form. The third describes the multiple-choice test derived from the large mass of experimental material. This short, objective test is designed for the use of psychologists, psychiatrists, educators, social workers and probation officers without any Rorschach training. In this part will be found special chapters on military psychiatric differentiation. The fourth part is composed of lists of the content of responses, intended for reference purposes.

Plaster of Paris Technique in the Treatment of Fractures and Other Injuries. By T. B. Quigley, M.D. 8th ed., cloth, 107 pp., with 103 illustrations. New York: The Macmillan Company, 1945. \$3.50.

This booklet describes, in a concise manner, the application of plaster of Paris to all parts of the body. Simple methods are given that require no special apparatus. The discussion of padding and of the complications that may arise when plaster casts are used is especially well done. Only one method is presented, which is probably an advantage to the novice, since it often requires long experience to select the most efficient technic for different disabilities. Whereas plaster can be used as described for splinting small joints like those of the finger, tin or aluminum is usually found to be much less awkward to manage.

Plaster technic is described for fractures and other injuries to the limbs only, but the technic can be applied to many other disabilities. This is an excellent book and should prove helpful to those who use this type of treatment.

Our Inner Conflicts. A constructive theory of neurosis. By Karen Horney, M.D. 8th ed., cloth, 250 pp. New York: W. W. Norton and Company, Incorporated, 1945. \$3.00.

This book, by an author who has proved her value as an interpreter of psychiatry, particularly the psychoneuroses, by her ability to present the material clearly and concisely for general reading, follows the tendency that has been characteristic of her writings in the past. The author has a clear concept of the subject and presents it in a comprehensive manner. She points out the harm that neurotic conflicts can inflict on the personality to resolve them, more than rational decision, evasion or the exertion of will power is

necessary. They can be cured only by changing the conditions within the personality that draw the conflict into existence. Dr. Horney's method of doing this is fully expounded, and, willing, however, to take an even broader view of therapy and writes as follows:

Fortunately analysis is not the only way to inner conflicts. Life itself still remains a very effective therapist. Experience of any one of a number of things may be sufficiently telling to bring about personal changes. It may be the inspiring example of a truly person, it may be a common tragedy which, by being the neurotic in close touch with others, takes him out of his egocentric isolation, it may be association with a so congenial that manipulating or avoiding them is less necessary. In other instances the consequent neurotic behavior may be so drastic or of such frequent occurrence that they impress themselves on the neurotic mind and make him less fearful and less rigid.

This, indeed, is sound psychotherapy and a point often overlooked by many writers on the subject. This book is highly recommended.

Pathology of Tropical Diseases. An atlas. By J. E. Ash, M.D., and Sophie Spitz, M.D. 4th ed., cloth, 350 pp., with 94 illustrations. Philadelphia: W. B. Saunders Company, 1945. \$10.00.

This volume presents an array of excellent photographic illustrations of many of the diseases of the tropics. The text that accompanies the illustrations is of uneven quality. That part dealing with pathology is excellent, but other parts are replete with statements that are of doubtful value, misleading or incorrect, and these detract from the value of the book.

The Eternal Ones of the Dream. A psychoanalytic interpretation of Australian myth and ritual. By Geza Róheim, Ph.D. 8th ed., cloth, 270 pp. New York: International Universities Press, 1945. \$4.50.

An anthropologic study from a psychoanalytic interpretation of various Australian myths, this book is divided into an introduction and twelve chapter headings, with a final summary and conclusion. There also appears a page of illustrations of several ritualistic ceremonies, as well as drawings depicting several myths and ceremonial objects. Especially frequent is the presentation and interpretation of native word symbols. This lends a heavy air of technicality to the work but makes for difficult reading to the uninitiated in psychoanalysis. The reasonableness of the author's interpretations depends on the reader's psychoanalytic leanings rather than on objective data. An example is the following statement: "The eternal ones of the dream it is we who deny decay, aggression and object-loss, and who guard eternal youth and reunion with the mother."

General and Plastic Surgery, with Emphasis on War Surgery. By J. Eastman Sheehan, M.D. 8th ed., cloth, 345 pp., with 15 illustrations. New York and London: Paul B. Hoeber, Incorporated, 1945. \$6.75.

This book, which was published in 1945, was not revised until October, 1946, and certain material is outdated by recent developments and concepts. One example is the recommendation that sulfonamide ointments be used in the treatment of burns, and another, that sulfonamide solution be used previous to closure of wounds.

This book, however, which has more to do with plastic surgery and the surgery of trauma than with general surgery, introduces and summarizes certain British contributions that should be of use in this country. Wounds are discussed generally and under the regions of the body in which they occur. An interesting section is devoted to war weapons and their methods of injuring and the injuries thus produced.

The volume is profusely illustrated with carefully selected diagrams and photographs.

Plastic surgeons and those interested in trauma may find this book a useful summary of the treatment of wounds during World War II, particularly the reconstructive aspects. It cannot be called a summary of all the methods developed during the war, however, for the procedures described are largely based on experiences in the Spanish Civil War and with the British in World War II.

The New England Journal of Medicine

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FEBRUARY 20, 1947

Number 8

TREATMENT OF INJURIES TO THE KNEE JOINT*

CLAY R. MURRAY, M.D.†

NEW YORK CITY

INJURIES to the knee joint may be discussed under the following three headings: diagnosis, treatment of surrounding structures and treatment of the joint itself. The third consideration, which is the most important, is the aspect of treatment which is usually neglected.

The basis of all treatment of the knee joint is an appreciation of the physiology of the knee and of how it is disturbed by injury to the joint. There is a mistaken idea that various ligaments stabilize the knee joint. The only two positions in which the ligaments stabilize the joints in living human beings are complete extension — as when one is standing in military attention — and complete flexion, as when one is in a full squat. These are unusual positions. It is perfectly true that in the cadaver, the ligaments stabilize the knee joint. This discussion, however, applies to the physiology of the knee joint in human beings, not to that in cadavers — in other words, to dynamic anatomy, not static anatomy.

In uninjured persons stabilization of the knee joint in any degree of flexion is accomplished by coordinated muscle action of the surrounding muscles. If, for any reason, that action is disturbed, so that one group of muscles acquires power superior to that of another, the knee joint becomes unstable, whether or not there is any lesion of the joint ligaments. The ligaments serve to prevent gross displacements.

I can state factually what happens when the knee joint is injured, but I cannot adequately explain it. Any injury to the intra-articular portion of the knee joint is associated with a rapid hypotonia that is relatively selective for the extensor mechanism of the joint and involves the rectus and the vasti muscles. The flexor group of muscles is also involved, but to a mild degree. The extensor group is implicated to such an extent that a palpable difference in tone can be demonstrated within two

hours after injury and visible evidence of atrophy is present within five days after injury. This point is too frequently not given adequate weight, mainly because the patient usually rolls up his trousers to disclose the knee joint. No patient should have anything covering his thighs during such an examination; he should be free of obscuring drapery from the hips down so that the thighs can be examined for any visible difference in size or contour, such as flattening of the rectus muscle, and palpated to determine the difference in tone, both in the relaxed state and in that of attempted contraction. The thighs should then be measured, at a definite level above a given anatomic landmark, so that the level will be exactly the same on the two sides. If there is no visible or palpable hypotonia or atrophy and no measurable atrophy, there is probably no lesion involving the knee joint, and it can be assumed that the lesion lies outside the joint. If there is palpable and visible hypotonia and measurable atrophy in the thigh muscles soon after injury, the difficulty lies within the joint. If that fact is remembered, one will already have gone a long way toward clearing up the diagnosis of obscure lesions in the knee joint.

The second point to remember is that any patient who develops fluid in the joint within hours of the injury does not have a traumatic synovitis but has a hemarthrosis. Whatever the diagnosis, it must explain the hemarthrosis. The habit of calling a collection of fluid within the knee joint a traumatic synovitis because no definite abnormality is observed is a serious mistake, because it implies that the joint has merely been irritated and that synovial fluid has collected. Synovial fluid collects in the knee joint over a period of days or weeks as a result of trauma, not over a period of hours. The condition must therefore be explained on the basis of bleeding into the joint.

The third point in diagnosis of these lesions is adequate examination, the first part of which consists in inspection, as pointed out above. Range of extension is a primary consideration. If the patient

*Presented at the annual meeting of the New Hampshire Medical Society, Manchester, May 14, 1946.

†Professor of orthopedic surgery, Columbia University College of Physicians and Surgeons, attending surgeon and chief of Fracture Service, New York Orthopedic Hospital.

epidemic of drug poisoning was brought to an end. Appendix B consists of selected articles bearing on drugs taken from the Federal Drug and Cosmetic Acts and Regulations. Appendix C is a summary of drug legislation now in force in eleven states and in New York City. The work concludes with the official rules of the Council on Pharmacy and Chemistry of the American Medical Association.

This new work should be in the collection of all public, medical and legal libraries and should be valuable for all persons interested in pharmacy and drug manufacturing.

Industrial Toxicology. By Alice Hamilton, M.D., and Rutherford T. Johnstone, M.D., director, Department of Occupational Diseases, Golden State Hospital, California. (Reprinted from *Oxford Loose-Leaf Medicine*, with the same page numbers as in that work.) 8^{vo}, cloth, 65 pp. New York: Oxford University Press, 1946. \$2.50.

This short monograph by recognized authorities summarizes the pathology, diagnosis, treatment and prevention of industrial poisoning. A long bibliography is appended to the text. The publishers in reprinting this important contribution have made it possible for interested persons to have the monograph without subscribing to *Oxford Loose-Leaf Medicine*. The monograph is recommended for all medical and public libraries and to all persons interested in industrial poisoning.

NOTICES

ANNOUNCEMENT

Dr Irving L. Pavlo, having returned from military service, announces the opening of his office at 469 Beacon Street, Boston, for the practice of ophthalmology.

SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, February 18, at twelve noon. Dr Reginald H. Smithwick will speak on "The Surgical Treatment of Hypertension." Physicians are cordially invited to attend.

BOSTON GASTROENTEROLOGICAL SOCIETY

The Boston Gastroenterological Society will hold a luncheon meeting for members and their guests in the Harvard Club on Wednesday, February 19, at twelve noon. Dr Dwight O'Hara will speak on "The Activities of the Massachusetts Medical Society."

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

The regular meeting of the New England Society of Physical Medicine will be held at the Hotel Kenmore, Boston, on Wednesday, February 19, at 8 p.m.

PROGRAM

Exercises for Bed Patients, Medical and Surgical. Dr J. Wayne MacFarland, of Washington, D.C., editor of *Life and Health* and vice-chairman on physical medicine, Southern Medical Association.

Physicians, students, physical therapists and nurses are cordially invited to attend this meeting.

NEW ENGLAND PATHOLOGICAL SOCIETY

The next meeting of the New England Pathological Society will be held on Thursday, February 20, at the Beth Israel Hospital, Boston. The afternoon slide seminar will be held at 4 p.m. Dinner will be served at the hospital, and the evening meeting will be held in the auditorium at 8 p.m. Dr Frank W. Foote will speak on the subject "Benign Proliferative Lesions of the Breast."

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

The three hundred and seventy-fifth meeting of the New England Ophthalmological Society will be held on Wednesday, February 19, at the Massachusetts Eye and Ear Infirmary, Boston.

PROGRAM

9:00 a.m.-12:00 p.m. Operating Clinic. Staff members.
2:30-3:30 p.m. Presentation of cases.
4:00-5:30 p.m. Instructional Course "Pathology of the Conjunctiva."
8:00 p.m. Business Meeting.
8:15 p.m. "Twenty-nine Cases of Rheumatoid Iritis." Dr Lloyd Mills.
8:45 p.m. "The Surgical Treatment of Strabismus in Children." Dr Maynard C. Wheeler, of the Eye Institute, Columbia Medical Center, New York City.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 20

FRIDAY, FEBRUARY 21

*9:00-10:00 a.m. The Mechanisms of Hemoglobinuria in Thermal Burns. Dr Thomas Hale Ham. Joseph H. Pratt Diagnostic Hospital.

*10:00 a.m.-12:00 p.m. Medical Staff Rounds. Peter Bent Brigham Hospital.

MONDAY, FEBRUARY 24

*12:15-1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, FEBRUARY 25

*12:15-1:15 p.m. Clinicoröntgenological Conference. Peter Bent Brigham Hospital.

WEDNESDAY, FEBRUARY 26

*9:00-10:00 a.m. The Use of Streptomycin in Tuberculosis. Dr Lowrey F. Davenport. Joseph H. Pratt Diagnostic Hospital.

*11:00 a.m.-12:00 p.m. Medical Clinic. Amphitheater, Children's Hospital.

*12:00 p.m. Clinicopathological Conference (Children's Hospital). Amphitheater. Peter Bent Brigham Hospital.

*2:00-3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater. Children's Hospital.

*7:15 p.m. Graduate Seminar in Pediatrics. Children's Medical Service. Amphitheater 3A. Massachusetts General Hospital.

*Open to the medical profession.

OCTOBER 11-MAY 14. Metropolitan State Hospital. Page 398. Issue of September 12.

FEBRUARY 18. South End Medical Club. Notice above.

FEBRUARY 19. New England Society of Physical Medicine. Notice above.

FEBRUARY 19. Boston Gastroenterological Society. Notice above.

FEBRUARY 19. New England Ophthalmological Society. Notice above.

FEBRUARY 20. New England Pathological Society. Notice above.

FEBRUARY 26. Tufts Alpha Omega Alpha. Page 156. Issue of January 23.

MARCH 11. Harvard Medical Society. Amphitheater. Peter Bent Brigham Hospital. 8:00 p.m.

MARCH 13. Cornell Medical Alumni Day. Page 156. Issue of January 23.

MARCH 13. What We Have Learned from the Study Through the United States of Child Health Service. Dr Warren R. Sisson. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

APRIL 28-MAY 2. American College of Physicians. Page 206. Issue of August 8.

MAY 20-22. Massachusetts Medical Society. Annual meeting. Hotel Statler, Boston.

JUNE 9-13. American Medical Association. Page 698. Issue of November 7.

JUNE 30-JULY 3. American Urological Association. Hotel Statler, Buffalo.

SEPTEMBER 8-12. Third American Congress on Obstetrics and Gynecology. Page 636. Issue of October 24.

DISTRICT MEDICAL SOCIETY

PLYMOUTH

FEBRUARY 20. Moore Hospital. Brockton.

MARCH 20. Goddard Hospital. Brockton.

APRIL 17. State Farm. Bridgewater.

MAY 15. Lakeville Sanatorium, Lakeville.

The New England Journal of Medicine

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Volume 236

FEBRUARY 20, 1947

Number 8

TREATMENT OF INJURIES TO THE KNEE JOINT*

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NEW YORK CITY

INJURIES to the knee joint may be discussed under the following three headings: diagnosis, treatment of surrounding structures and treatment of the joint itself. The third consideration, which is the most important, is the aspect of treatment that is usually neglected.

The basis of all treatment of the knee joint is an appreciation of the physiology of the knee and of how it is disturbed by injury to the joint. There is a mistaken idea that various ligaments stabilize the knee joint. The only two positions in which the ligaments stabilize the joints in living human beings are complete extension — as when one is standing at military attention — and complete flexion, as when one is in a full squat. These are unusual positions.

It is perfectly true that in the cadaver, the ligaments stabilize the knee joint. This discussion, however, applies to the physiology of the knee joint in human beings, not to that in cadavers — in other words, to dynamic anatomy, not static anatomy.

In uninjured persons stabilization of the knee joint in any degree of flexion is accomplished by co-ordinated muscle action of the surrounding muscles. If, for any reason, that action is disturbed, so that one group of muscles acquires power superior to that of another, the knee joint becomes unstable, whether or not there is any lesion of the joint ligaments. The ligaments serve to prevent gross displacements.

I can state factually what happens when the knee joint is injured, but I cannot adequately explain it. Any injury to the intra-articular portion of the knee joint is associated with a rapid hypotonia that is relatively selective for the extensor mechanism of the joint and involves the rectus and the vasti muscles. The flexor group of muscles is also involved, but to a mild degree. The extensor group is implicated to such an extent that a palpable difference in tone can be demonstrated within two

hours after injury and visible evidence of atrophy is present within five days after injury. This point is too frequently not given adequate weight, mainly because the patient usually rolls up his trousers to disclose the knee joint. No patient should have anything covering his thighs during such an examination; he should be free of obscuring drapery from the hips down so that the thighs can be examined for any visible difference in size or contour, such as flattening of the rectus muscle, and palpated to determine the difference in tone, both in the relaxed state and in that of attempted contraction. The thighs should then be measured, at a definite level above a given anatomic landmark, so that the level will be exactly the same on the two sides. If there is no visible or palpable hypotonia or atrophy and no measurable atrophy, there is probably no lesion involving the knee joint, and it can be assumed that the lesion lies outside the joint. If there is palpable and visible hypotonia and measurable atrophy in the thigh muscles soon after injury, the difficulty lies within the joint. If that fact is remembered, one will already have gone a long way toward clearing up the diagnosis of obscure lesions in the knee joint.

The second point to remember is that any patient who develops fluid in the joint within hours of the injury does not have a traumatic synovitis but has a hemarthrosis. Whatever the diagnosis, it must explain the hemarthrosis. The habit of calling a collection of fluid within the knee joint a traumatic synovitis because no definite abnormality is observed is a serious mistake, because it implies that the joint has merely been irritated and that synovial fluid has collected. Synovial fluid collects in the knee joint over a period of days or weeks as a result of trauma, not over a period of hours. The condition must therefore be explained on the basis of bleeding into the joint.

The third point in diagnosis of these lesions is adequate examination, the first part of which consists in inspection, as pointed out above. Range of extension is a primary consideration. If the patient

*Presented at the annual meeting of the New Hampshire Medical Society, Manchester, May 14, 1946.

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is seated, with the heel of the extended leg on the examiner's knee, and told to relax, the knee joint either goes into complete extension or remains in partial flexion. Persistent flexion is due either to muscle spasm or to mechanical blocking in the joint. Flexion caused by muscle spasm may be secondary to fluid in the joint, which can be pushed into full extension without severe pain under slow pressure, on release of the pressure, the knee rebounds into flexion. The normal knee in full extension never rebounds when the pressure is released. If the joint cannot be brought into full extension by steady, slow, continued pressure because of either mechanical obstruction to extension or the severity of the pain occasioned, more than muscle spasm or fluid is involved — there is probably a mechanical derangement of the knee joint.

I find it utterly impossible to make an exact differential diagnosis when confronted with the various mechanical derangements of the knee joint that can occur. A diagnosis of mechanical derangement of the knee joint is made on the basis of the following: a history of injury, hypotonia in the thigh muscles, with or without atrophy, depending on whether hours or days are involved, the rapid accumulation of fluid after injury, and inability to hyperextend the knee joint slowly and gradually into extension, as pointed out above. The injury may be a torn meniscus, a pinched fat pad, which is incidentally a real lesion, or a strain of the ligaments — that is, a mechanical derangement outside the knee joint. Sprains of the ligaments, unless accompanied by hemarthrosis, are not accompanied by hypotonia and loss of thigh contour. When actual ligamentous tears occur they are evidenced by abnormal mobility of the joint in full extension — that is, the leg can be abducted on the thigh if the internal collateral ligament is torn and adducted if the external collateral ligament is torn. In the normal knee, neither abduction nor adduction of the leg on the thigh in full extension is possible, nor is rotation of the tibia on the femur in full extension or forward or backward movement of the tibia on the femur in flexion. The integrity of the various ligamentous structures can thus be tested.

Another frequent lesion is that involving the crucial ligaments, which is a less serious injury than those described above. In the last twenty years this injury was observed at operation in an appreciable percentage of cases, and surgical repair was undertaken in extremely few. I have never seen a patient with a tear of the anterior crucial ligament who, on the basis of a three-year follow-up study, showed any physiologic disturbance of joint function if the quadriceps mechanism had been restored by active treatment, although Dr. John Royal Moore, of Philadelphia, has told me of a case in a boxer, who depended on his footwork for success, in which surgical intervention was necessary.

The posterior crucial, which is the more important ligament, keeps the femur from going unduly forward during weight bearing, the anterior merely keeps it from going backward in hyperextension — an unusual situation. During walking, the tendency is for the femur to slide forward on the tibia when the knees are flexed and weight is borne. The posterior crucial ligament therefore has more functional value than the anterior crucial. The posterior crucial ligament is completely torn when complete dislocation of the knee joint occurs. It is a startling fact that in such dislocation marked instability after reduction and restoration of the muscular mechanism of the thigh is not a characteristic finding.

I therefore recommend much less attention to injuries of the crucial ligaments than is usually accorded them. They represent an internal derangement of the knee joint, without mechanical block. But, more to the point, they represent loss of tone and atrophy in the quadriceps group of muscles, which should be the center of attention for treatment.

Simply because the diagnosis of injury to the knee joint has been made is no reason for an operative procedure. The real physiologic disturbance is hypotonia and atrophy of the quadriceps group of muscles. Attention should be centered on that disturbance.

The number of operations devised to repair ruptures of the crucial ligament is legion. Each one has been devised because the preceding ones have proved to be unsatisfactory. And the end is not yet in sight. The point of attack is wrong, emphasizing a torn structure rather than the physiologic disturbance created by the injury. The less operating done on crucial ligaments and the more attention devoted to restoring tone and power to the quadriceps group, the better off the patient will be. In other words, these injuries, in my opinion, call for constructive conservative therapy — I regard the terms "intelligent" and "constructive," as synonymous.

The diagnostic feature of meniscus injury is a sudden, twisting effort, with the knee flexed, that results in localized pain on the inner or outer side of the knee joint, followed sometimes (but not always) by a rapid accumulation of fluid. Tenderness at the site of the pain, with or without locking of the knee joint, is observed. When the cartilage separates, it may tear loose from its ligamentous attachments to the edge of the tibia, in which event the rupture is through vascular connective tissue. The cartilage may be displaced within the joint. If it remains within the joint, there is a mechanical locking, and the knee will not fully extend because a block of fibrocartilage lies between the tibia and the femur, full extension cannot be obtained, even with an anesthetic. Such a joint must be unlocked. It is pointless to immobilize such a joint in the

locked position. Before it is immobilized, if that form of therapy is to be used, the joint must be unlocked by operation or by manipulation. I do not believe that operation should be performed on a patient with a primary injury until manipulative reduction has been tried. Any manipulation should be done under an anesthetic, for several reasons. In the first place, the patient's muscles must be completely relaxed — otherwise, there is muscle resistance to the manipulation, and failure is probable. Secondly, under anesthesia the manipulation can be more carefully done, repeatedly if necessary, with a minimum of trauma to the joint. Thirdly, the manipulation under anesthesia will not cause pain and distress to the patient, increasing his protective reflex safeguarding the joint and interfering with later functional activity.

The method of reduction is simple. The hip and knee are flexed at right angles. The tibia is rotated loosely inward and outward on the femur in the flexed position, under anesthesia. I prefer intravenous anesthesia because it gives excellent relaxation. Having employed rotation, one loosely abducts and adducts the tibia on the femur in the flexed position. Following this, the knee is brought into sudden extension. The purpose is the same as in shelling peas: the pea is popped out of the pod by pressure between the fingers. The meniscus is the pea, the joint is the pod, and the femur and the tibia are the two fingers. Once the cartilage has been "popped" from its locked position to the periphery of the joint, it cannot go back into the joint as long as the knee is extended.

If the patient's knee is not locked, although he has the signs of a meniscus tear, I believe in radical surgery, in the sense that any procedure undertaken should be complete and thorough. I also believe that any surgeon who performs an unnecessary operation is foolish. No patient with a meniscus lesion whose knee joint is or can be unlocked should be operated on for a first injury. I admit that, on the basis of paper logic, operation is the wisest and most sensible procedure. Once the meniscus is removed, there should never be any more trouble. Perhaps some surgeons never have complications after a knee-joint operation. I sometimes do. Some patients never get pneumonia, or atelectasis or thrombophlebitis and embolism. But some do. Some patients are successful in restoring quadriceps function and stability after operation. But some are not. If the knee joint in a case of primary injury cannot be unlocked the patient should be operated on — not within a week or a month, but as soon as possible.

When the joint can be unlocked or has never been locked and the meniscus is probably involved because of the symptomatology, the knee joint must be kept extended. No activity should be permitted in a patient with a knee joint that is moving, because constant movement will cause continuous damage.

On the other hand, the quadriceps group of muscles is developed solely by exercise. The surgeon seems to be between the devil and the deep sea — the patient cannot exercise his knee, but he must develop his quadriceps.

The problem is not too difficult. The patient must be kept from moving his knee, but he must be made to walk. A plaster or other encasement from ankle to groin in extension does the former, and every hour or oftener, he walks progressively increasing distances without crutch or cane. The substitute for such co-ordinated muscular activity is the quadriceps-contraction exercise — a substitute, but a poor one, because it exercises only the quadriceps group of muscles. What is desired is co-ordinated action by all the muscles of the thigh. When the patient contracts the quadriceps, he selectively exercises a single group of muscles. This is not physiologic quadriceps function. Walking with the knee immobilized must be practiced long enough for the torn ligamentous attachments to reattach, roughly for four weeks, then the plaster is removed, and normal function is started. If the procedure is properly carried out, the patient does not add the atrophy occasioned by disuse to the primary reflex atrophy and hypotonia. He exercises the quadriceps group of muscles as part of a co-ordinated muscle action, and as a result he does not have a weak and atrophied thigh and does not complain that if he turns suddenly his knee "goes out" from under him.

The "giving way" of the knee is usually due not to a residual lesion in the joint but to the facts that muscle support of the joint is inadequate in the quadriceps group and that the joint is thereby rendered unstable. When the plaster encasement is removed the patient is not taught to bend his knee but to develop extensor power, which is where his defect lies. His flexor power is unimpaired.

What is it that makes immobilized joints stiff? There is a good deal of vague and misleading talk about contractions and adhesions. Actually, the patient is suffering from loss of elasticity in and thickening of the capsular structures. This results from loss of efficiency of the minute circulation, secondary to absence of normal muscular activity — the essential factor in maintaining the circulation at an efficient level. A joint does not have to move to remain supple and limber. The muscles that ordinarily move the joint must be kept moving for the minute circulation of the part to approach normal. Ligaments will not be thickened and lose elasticity, leading to stiffness, nor will the mesotenon and paratenon become thick and inelastic secondary to circulatory stagnation.

A tendon does not lie loose and unconnected with the surrounding tissues. It moves because the soft parts — represented by mesotenon or paratenon — are thin, extremely elastic and almost weblike. If they are subjected to chronic vascular stasis, a

cirrhosis is, in effect, produced, with a thickening of the structure and loss of elasticity

The problem is not one of adhesions or contractions but one of circulation, particularly of the minute circulation. That is why normal and co-ordinated muscular activity is so important, apart from its function in the stabilization of the joint.

When the plaster encasement is removed in a case of knee-joint injury, the patient must extend his knee. When he is being taught to walk, instead of being told to be sure to flex the knee at each step, he is instructed to push the knee backward at each step. This is a means of making the quadriceps muscle work. The flexion function returns routinely on normal use.

Straight-leg raising is another excellent method of cultivating extensor function. But the best one is walking, which is a normal and co-ordinated muscle exercise. The patient is not concerned with the action of individual muscles, he practices co-ordinated action of the whole muscle group. (It may sound as though I am making a great deal out of a minor point, this is actually a major point, involving the whole basis of a normal physiologic functional exercise.)

If a patient with a knee joint must be operated on because of the nature of the original injury or because conservative therapy, as described, has failed, what should be done? I have been impressed over the years with the folly and impracticability of making a clear-cut and definite diagnosis in cases of internal derangement of the knee joint. I know that there are those who believe that the definite diagnosis of a single and specific lesion can be made, *I am not among them*.

When a knee joint is operated on for internal derangement, which is as far as I am willing to go in making a diagnosis, I explore the joint thoroughly. I do not make a peephole incision for removal of the meniscus, if that seems the probable difficulty. It can be done simply, of course. Instead, the joint is exposed from top to bottom. I operate without a tourniquet, since I do not believe that temporary anoxemia is of any help to the tissues. A high Trendelenburg position, to further adequate venous return, without a tourniquet, is accompanied by little bleeding.

After a parapatellar incision from the tibial margin to the upper limit of the suprapatellar pouch the patella is displaced to the outer or inner side of the joint. The knee joint is then flexed over the table, enabling visualization of the whole joint and permitting attempts to correct all pathologic conditions observed.

In a series of over 400 cases in which knee joints were so explored, injury to the internal meniscus alone occurred in only 30 per cent. In another 30 per cent at least one other lesion, such as a torn crucial ligament, a lesion of the synovial membrane or a fat-pad lesion, was discovered. In 40 per cent,

from three to nine lesions in addition to that of the meniscus were observed.

Operation in these cases is therefore performed through a long, generous incision, which heals from side to side, not from end to end. The long incision has the same healing time as the short one, and does not entail any difference in postoperative regime from that used with a short incision.

It has been held by some that the knee joint must be kept perfectly quiet postoperatively because movement of the soft parts will interfere with healing. It is interesting that most studies of wound healing are made on the abdominal wall, which is under constant movement twenty-four hours a day with every respiratory movement, it cannot be kept quiet. But there is normally no difficulty in healing of the abdominal wall. It is true that if the patients cough, vomit or sneeze, the wound may not heal properly. The situation is identical in the knee joint. The knee joint can be kept moving but, metaphorically speaking, cannot be allowed to cough, sneeze or vomit. Overpushing of the joint movement, the use of violent or forced exercise, exercise to fatigue limits or beyond pain limits are contraindicated. But healing is aided by movement within physiologic limits. The joint should never be immobilized postoperatively—one of the reasons why knee-joint injuries and operations are associated, in the lay mind, with stiff knees is the fact that for many years it was routine to immobilize knees postoperatively for considerable periods. I am sorry to say that in some places this is still done. If a knee joint is immobilized postoperatively, there must be a valid excuse for the procedure, and the excuse cannot be the problem of wound healing. There is a physiologic limit to the amount of exercise permissible. In general, however, the more exercise obtained for the muscles activating the knee joint within those limits, the better off the patient.

When an injury to the meniscus has cleared up under conservative treatment and the joint is again injured two or three or more months later, the same conservative treatment is not repeated. If the meniscus tear involves the ligamentous structures uniting the meniscus to the margin of the tibia, it will practically always heal under the conservative treatment I have described. If the tear, however, is through the cartilage itself, as in a so-called "bucket-handle fracture," in which the tear runs the length of the cartilage, or if a tab is torn loose from the edge of the cartilage, the chances are that the lesion will never heal. That is a broad statement, but on the basis of all the evidence reported to date, a tear limited to the meniscus will not heal, although it usually heals if it is through the ligamentous structure. If, therefore, under conservative therapy for a supposed torn meniscus the patient becomes free from symptoms, and later has a recurrence of symptoms, it is to be assumed that the tear is through the cartilage and has not healed under

conservative treatment. The patient is then a fit subject for operation

To make assurance doubly sure, is it wise to wait for multiple recurrences before resorting to operation? Such a course is the equivalent of locking the stable door long after the horse has escaped. By the time a patient has sustained such multiple incidents, he has badly damaged the articular cartilage of the joint. Such misguided conservatism simply contributes to progressive damage of the knee joint.

Although I am opposed to operating on a patient with a primary injury of the meniscus if the joint can be unlocked, there is no question in my mind that a second incident, and not the eighth or ninth, is the indication for operation. Conservative therapy is wasted on recurrences of the original injury.

DISCUSSION

DR. EZRA A. JONES (Manchester) I should like to ask concerning the value of treatment with x-rays. Do you think that air injection is of any value? Also, what is the percentage of injuries to the lateral meniscus as compared with those to the medial meniscus, if there is the same damage?

DR. MURRAY On the question of air injection, for the last twenty years, I have tried air injection, oxygen injection and air or oxygen combined with other roentgenographically demonstrable substances. The net result has been to make the problem of injuries to the knee joint doubly confusing, because of the extra shadows that the injection of air and opaque material demonstrates. Recently, in Sweden, a technic was developed by which air is injected and x-ray examination is made by coning down to a small concentrated area, such as the internal meniscus and the intercondylar notch, and the claim is made — I have seen some of the pictures, and I am investigating some of them now — that by that technic more specific abnormalities can be demonstrated. I am attempting to duplicate that story, otherwise, my experience is that all that air injections have done is to confuse the picture.

Regarding the question about the relative percentage of injuries to the internal and the external meniscus, roughly 15 per cent of cases occur in the lateral meniscus. Whenever the diagnosis of a lesion of the internal meniscus is made the joint is thoroughly investigated, 10 per cent of cases are bilateral. About 5 per cent of all meniscus lesions occur in the external meniscus alone.

DR. ALBERT P. LAFRANCE (Laconia) I should like to ask Dr. Murray if, when he encounters an injury of the fat pad, he removes the fat pad extensively or treats the case conservatively, with the idea that the lesion may subside.

DR. MURRAY Fat-pad injuries have the same history that one ordinarily gets with a meniscus lesion. There is tenderness alongside the patella tendon and far forward on the joint line, right at the edge of the patella tendon. All the cases are treated conservatively for the first incident — that is, by resting the joint but at the same time exercising the muscles as described above and by enforced walking in plaster, followed by the development of the quadriceps muscle later. With a second occurrence — in other words, a second pinching incident — the joint is explored, the fat pad is removed and the patient is treated postoperatively as for any knee-joint injury.

A PHYSICIAN I am in accord with the stressing of the restoration of the quadriceps muscle for strength and function. I must admit that I believe in contraction to some extent, in addition to all the other things, such as early motion and normal use. I believe in exercising the quadriceps muscle, especially in teaching the patient to control the muscle while he is still in bed. Actually, I prefer to have the patient do quadriceps exercises preoperatively, to learn to use the muscle, and then learn to walk.

DR. MURRAY The exact criteria employed in this routine should be stressed. As pointed out above, the knee joint should not be permitted to "cough" or "vomit" or "sneeze". By this I meant that premature weight bearing is comparable to coughing or sneezing after abdominal operations.

I like to let patients walk on the third day, I have had some who walked on the second day, and many walk only on the sixth or seventh day. None of them are immobilized. I try to get them to do straight-leg raising, muscle exercises and actual walking.

DR. ROBERT R. RIX (Manchester) A diagnosis of internal derangement of the knee joint should not be lightly made, as Dr. Murray pointed out because it is disconcerting to operate on a knee joint and not find anything. Of course, when a knee joint with a bucket-handle tear is opened, the injury is visible. But if the tear is in the posterior portion of the cartilage, out of sight, it cannot be seen. And it is therefore extremely important to make the diagnosis of the tear in the posterior end of the meniscus, so that the knee joint can be entered with confidence and the cartilage removed.

I want to ask Dr. Murray on what criteria he bases the diagnosis of posterior tear of the meniscus.

DR. MURRAY (closing) The diagnosis is revealed by pain back of the knee joint on attempts to straighten the knee and by a point of tenderness behind the internal collateral ligament. This situation is one of the reasons why an incision allowing complete exploration of the joint is made. The incision starts at the top of the quadriceps pouch and is brought down around the border of and 2.5 cm. away from the patella, and then down practically to the tibial tubercle. The patella is displaced outside or inward. The anterior two thirds of the cartilage can be examined through the incision when the knee joint is fully flexed. The fat pad is then removed — it is completely removed in every knee-joint exploration. Operation is performed specifically for a fat-pad lesion, of course, but the pad is removed as a routine in operation for any other lesion because, if it is out, it can never subsequently be pinched, and because its removal permits a wide view of the joint, which is otherwise seriously handicapped by the fat pad, particularly if it is large.

With a history and a suspicion of a tear that cannot be seen, particularly in cases in which repeated incidents have occurred, the posterior part of the joint is explored. Formerly, such exploration had to be done through a separate incision, alongside the hamstrings. But recently, instead of the parapatellar incision, the incision is begun at the top of the quadriceps pouch and is a semicircular one that comes around the lateral or mesial aspect of the knee joint and forward to the tibial tubercle below the patella. This has two advantages. The skin incision lies over the lateral aspect of the joint, and exercise does not increase the tension on the sutures. The anterior skin flap is dissected forward, and the anterior capsule incision can be made close to the patella. If no lesion of the cartilage is observed, the capsular incision is closed and the joint is opened behind the collateral ligament, the posterior portion of the cartilage being inspected. Thus, only one skin incision — and therefore one source of infection — is involved.

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formed before permanent changes occur in the vessel walls, should improve the renal hemodynamic state.

It has been argued that since splanchnicectomy does not lower the blood pressure when metal clamps are constricting the renal vessels in dogs, it cannot improve renal circulation in man. Such reasoning is fallacious. How could the blood flow be increased by a sympathetic denervation when a mechanical obstruction still exists? I believe that in hypertension in human beings there is a neurogenic clamp—a more or less continuous vasoconstriction—and that section of the autonomic nerves to the blood vessels removes this neurogenic clamp and prevents further abnormal constriction of the arterioles.

It has repeatedly been proved that in hypertension there is a decrease in renal blood flow, and our work, using inulin and Diodrast, has shown that after splanchnicectomy in such cases the renal blood flow has been definitely maintained despite a reduction in blood pressure.³ This suggests an increase in renal blood flow. Work being carried on at present tends to substantiate this hypothesis. This is considered the rationale for the surgical treatment of hypertension.

SURGICAL PROCEDURES

The surgical technic for the treatment of arterial hypertension differs in various clinics, chiefly in the extent of sympathetic denervation. The least extensive is the subdiaphragmatic splanchnicectomy of Adson⁴ and Craig.⁵ Considerably more extensive is the bilateral supradiaphragmatic splanchnicectomy that I⁶ have been carrying out for the past thirteen years. A somewhat more complete denervation is that of Smithwick,⁷ which really combines the two operations mentioned above. A much more extensive denervation is produced by the nearly total sympathectomy of Grimson.⁸ Just which of these procedures will finally be adopted cannot at present be determined. We have carried out the bilateral supradiaphragmatic splanchnicectomy in over 1500 patients, and are not convinced that additional denervation is necessary.

The operation that we perform consists in the bilateral resection of a long segment of the greater splanchnic nerves. This excision extends from the level of the seventh dorsal vertebra downward through the diaphragm. In many cases traction on the greater splanchnic nerve before it is divided pulls the celiac ganglion up to the diaphragm, so that the excision actually extends to the celiac ganglion. In addition, the lower thoracic sympathetic ganglions—usually, the eighth, ninth, tenth, eleventh and twelfth and frequently the seventh as well—are excised. The bilateral removal of the ganglions, of course, includes the various lesser and least splanchnic nerves arising from them. There is always a dramatic and immediate drop in the blood pressure, which may rise in the course of a few hours to a

normal level. Generally, the pressure fluctuates more or less widely for varying periods of weeks to months before it becomes stabilized. In a few cases the pressure remains normal from the beginning.

The bilateral procedure is carried out at one operation, and the time consumed varies from forty-five minutes to an hour and a half. The patient is not shocked by this procedure, although the blood pressure may drop remarkably. In some cases it is necessary to give Neo-Synephrin during the second half of the operation and occasionally for the first few hours thereafter. Patients are encouraged to sit up at an early date, and most of them are out of bed within a week. When the upright position is first assumed, there may be a postural hypotension. This as a rule corrects itself within a few days. Bandaging of the legs and compression of the abdomen have never been found necessary. The usual stay in the hospital is two weeks following operation. Many patients are able to resume their normal activities five or six weeks following the procedure. In fact, some return to their regular work within four weeks of the operation, but a rest period of four weeks at home is advised.

CRITERIA FOR OPERATION

The selection of patients for the surgical treatment of hypertension has been arrived at by the trial-and-error method. When this type of therapy was first undertaken, nothing was known regarding the possibilities or the end results. We therefore operated on patients for whom today surgery would be refused. Age is a definite factor. The highest percentage of cases with sustained worth-while lowering of blood pressure occurs in patients under thirty years of age. In this age group, favorable results were obtained in nearly 80 per cent of cases. In the older age groups, only about 50 per cent of the patients have shown worth-while continued improvement. The youngest patient operated on for hypertension was eight and the oldest sixty-one years of age. Operation is usually not recommended in patients over fifty-three. Exceptions are occasionally made—for example, relief of symptoms is almost certainly obtained irrespective of lowered blood pressure. We have therefore operated on a few patients of fifty-four to fifty-eight years of age whose symptoms were so incapacitating that relief alone justified the surgical procedure. In these cases symptomatic relief was obtained, but in many the blood pressure was not significantly affected. In one patient over sixty years old, operation was performed because of a rapid loss of vision, with extensive hemorrhages and exudates in both fundi. This patient had complete restoration of vision, which has been maintained over a postoperative period of seven years, although the blood pressure was not significantly affected.

All patients are thoroughly studied in various clinics of the hospital so that the condition of the

RESULTS OF BILATERAL SUPRADIAPHRAGMATIC SPLANCHNICECTOMY FOR ARTERIAL HYPERTENSION*

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ARTERIAL hypertension, usually designated as essential hypertension, is a highly complex disease syndrome. Its manifestations are many and varied, making a true evaluation of any form of therapy extremely difficult. This is further complicated by the normal progress of the disease, which encompasses the extremes from a fatal termination in a few months to a seemingly benign course of many years. Arterial hypertension is never actually benign, however, and the term should not be used. Sooner or later, damage to the brain, heart or kidneys will surely result. The term "essential" is also a misnomer. The elevation of the blood pressure is not necessary, as was at one time believed, to ensure an adequate blood supply to the various organs of the body in the presence of arteriosclerosis.

Although the disease may principally affect the brain in one patient, the heart in another and the kidneys in a third, in all the common factor is a more or less continuous elevation of the blood pressure, both systolic and diastolic. An increase in the blood pressure — temporary, recurrent or continuous — can, of course, occur with a wide variety of pathologic conditions, such as cerebral trauma, basophilic adenoma of the pituitary body, adrenal tumors, coarctation of the aorta and chronic nephritis. In 1939 Page¹ listed forty-seven conditions causing or associated with an elevated blood pressure. The diagnosis of arterial or essential hypertension is really made by exclusion of all the other conditions that may present a somewhat similar picture. This paper considers only the surgical treatment of what is usually designated as "essential hypertension" and in its severer form, "malignant hypertension."

RATIONALE FOR SURGICAL TREATMENT

The rationale for the surgical treatment of hypertension is dependent on one's conception of the disease, especially of its etiology. No one has yet been able definitely to establish the actual cause of arterial hypertension. I have accepted the renal humoral theory, best demonstrated by the brilliant experiments of Goldblatt,² who has conclusively shown that renal ischemia, or at least interference with its hemodynamic state, produces a continuous elevation of blood pressure without evidence of impaired renal excretion. Numerous workers have

shown that such interference with the blood supply of the kidneys results in an excessive amount of a renal pseudoglobulin called "renin," which reacts with another pseudoglobulin, probably from the liver, named "preangiotonin" (the "renin-activator" of Page¹) to form an active vasopressor substance called "angiotonin." This causes arteriolar constriction of sufficient degree to raise peripheral resistance throughout the body, with consequent elevation of blood pressure.

Numerous causes for a primary renal ischemia may exist, but I believe that in the majority of cases it is of neurogenic origin. It has been demonstrated experimentally that electric stimulation of the splanchnic nerves elevates blood pressure, presumably by constriction of the arterioles in the kidney, with resulting renal ischemia. It is my opinion that in human hypertension excessive stimulation through the splanchnic nerves causes similar changes in the renal hemodynamics. This abnormal stimulation of the splanchnic nerves originates, of course, in the autonomic centers of the brain. The activating stimulus may be psychic, reflex from stimuli originating in various parts of the body or chemical. It is known that normally such stimuli are constantly influencing the sympathetic nervous system. How, then, can one explain the abnormal excessive response, sufficient to cause a renal ischemia? I believe that it is a congenital abnormality in the autonomic nervous system whereby excessive responses are evoked by normal stimuli. In the majority of hypertensive patients this congenital tendency of the autonomic system to over-react — that is, to respond to a given stimulus by either greater or more prolonged vasoconstriction — is apparently inherited.

I believe that Raynaud's disease presents a comparable condition. Here, excessive responses to normal stimuli of the autonomic nervous system result first in repeated abnormal vasoconstriction of the peripheral vessels in the hands and feet. Later, with more continuous constriction, permanent vascular changes leading to gangrene occur. No one doubts the role of the autonomic nervous system in Raynaud's disease, since there is definite visual evidence of vasoconstriction following psychic stimuli or exposure to cold. My hypothesis is that in hypertension similar stimuli acting on the abnormally sensitive autonomic centers for the splanchnic nerves cause a more or less continuous renal ischemia. If this theory is correct, — and there is considerable evidence to support it, — splanchnicectomy, if per-

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From the Section of Neurosurgery, University of Michigan Medical School and Hospital.

†Professor of surgery, University of Michigan Medical School, chief Neurosurgical Section, University of Michigan Hospital.

adopted, however. A patient under fifty years of age who has completely recovered from one or more cerebrovascular accidents does not present an unusually high surgical risk. If other findings are favorable, we recommend operation and with a definite hope of preventing another stroke. The presence of severe brain damage, as evidenced by aphasia or hemiplegia, is certainly a contraindication to this operation.

Evidence of cerebral encephalopathy manifest by mental confusion or loss of memory presents a difficult problem in deciding for or against surgery. If the mental changes are recent, especially if they are mild, a complete return of cerebral function to a normal status may be expected following splanchnicectomy. On the other hand, if the mental confusion and loss of memory are marked and of long duration, improvement cannot be expected, and operation is not recommended. Even if the changes are mild but apparently due to small repeated cerebrovascular thromboses, I believe that operation should not be performed.

Obesity is a frequent finding in hypertensive patients but, unless extreme, cannot be considered a definite contraindication to splanchnicectomy. It does, however, place an additional load on the heart which has perhaps already been damaged, and certainly makes the operation more difficult and the convalescence more uncomfortable. We therefore recommend a low-calorie diet and do not generally advise operation until the weight has been significantly reduced.

Malignant hypertension, provided the cardiac and renal damage is not far advanced, is, in our opinion, a definite indication for splanchnicectomy, although in some clinics it is considered a contraindication. We classify as malignant only the cases showing a definite papilledema. The fundusoscopic examination usually reveals hemorrhages, exudates and severe angiospasm. The blood pressure is high, especially the diastolic, and most cases show moderate to severe cardiac and renal damage. Without operation the prognosis in these cases is hopeless, a large percentage of the patients dying within the first year.

In summary, the following are our criteria for operation: a patient below fifty-four years of age, a more or less continuously elevated blood pressure, with a systolic pressure over 170 and a diastolic pressure above 105, a nonprotein nitrogen below 45 mg and preferably below 40 mg per 100 cc, a well compensated heart, and a relatively normal cerebral function. Exceptions are occasionally made, especially in the older age group and in cases with a slightly higher nonprotein nitrogen. These exceptions are generally made because of incapacitating symptoms, such as excruciating headaches, or when there is evidence of an otherwise hopeless malignant hypertension.

CLASSIFICATION OF HYPERTENSION

The evaluation of the surgical treatment of hypertension by bilateral supradiaphragmatic splanchnicectomy involves many factors. This is due to the varied manifestations of the disease. It must be remembered that arterial hypertension is a generalized disease, all organs of the body being affected, in some patients the clinical evidence of cerebral damage predominates, in others the heart is chiefly affected, and in some impaired renal function is the chief concern. Any combination of these may occur to complicate the picture further. In addition, the eye findings may give evidence of severe hypertension without cardiac or renal injury. Symptoms are absent in some patients, but are predominant in others. For these reasons a new classification, based on the dominant finding has been suggested,⁹ as follows:

Group 1 (with early, mild hypertension) These patients are entirely asymptomatic, have normal or slightly abnormal fundi and show no evidence of cardiac, renal or cerebral involvement.

Group 2 (in which symptoms are predominant) All patients in this group complain of symptoms and have mild changes in the retinal blood vessels, but display no evidences of cardiac, renal or cerebral impairment.

Group 3 (in which organic heart disease is predominant) In each case the diagnosis of heart disease is confirmed by either a definitely abnormal electrocardiogram or a teleroentgenogram showing cardiac enlargement, or both.

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RESULTS OF OPERATION

The majority of our patients have been studied at postoperative periods ranging from one to twelve years. We do not believe that earlier studies have valuable significance.

Symptomatic relief has been striking. Excruciating headaches, usually suboccipital, marked nervousness and irritability, insomnia and distressing palpitation have been greatly relieved or completely eradicated in 86 per cent of the patients still living. This percentage of improvement has persisted almost unchanged over postoperative periods of five to twelve years. Such symptomatic relief is not necessarily dependent on a significant lowering of the blood pressure or improvement in cardiac or renal function.

heart, kidneys, cerebral blood vessels, and eyes can be evaluated as accurately as possible. The blood pressure is taken in both arms and generally in one leg in the horizontal, sitting and upright positions, but for purposes of comparison with the postoperative group, only the sitting readings are considered. These are made at least three times in each arm at one examination, and during the three days of special studies repeated blood-pressure records are made. Careful eye examination, including the fundi and visual fields, is made in the ophthalmologic department. The cardiac status is determined by the electrocardiogram, orthodiagram and teleoroentgenogram. Due consideration is given, of course, to any pertinent facts in the history suggesting previous cardiac insufficiency, such as nocturnal dyspnea, severe exertional dyspnea and angina. We much prefer a negative cardiac history, since the majority of deaths five to thirteen years postoperatively have occurred in patients giving a definite preoperative history of heart complications. Cardiac decompensation is a definite contraindication to surgery. If the cardiac status improves under bed rest, digitalization and other therapeutic measures, however, operation is recommended in the majority of cases. These patients are warned that although the heart may show marked improvement following splachnicectomy, they must continue to be careful and not overexert themselves or place additional loads on an already damaged heart muscle.

Recent evidence of a coronary occlusion is also a contraindication to surgery. We have, however, operated on many patients with a previous history of coronary occlusion when the cardiac status seemed adequate. The operative risk in such patients is not greatly increased, but the prognosis for a longer postoperative life is poorer.

Gross enlargement of the heart, although definitely increasing the operative risk, is not in itself a contraindication. Many patients with enormous enlargement of the heart have shown striking reduction in cardiac size, even to normal, following the reduction in blood pressure by splachnicectomy.

The renal status is determined by an eighteen-hour concentration test, as well as studies of urea clearance and blood nonprotein nitrogen, and urinalysis. In addition, intravenous pyelograms are made in all cases to rule out gross abnormalities in one or both kidneys. If these are unsatisfactory, retrograde pyelograms are made. Markedly contracted kidneys, polycystic kidneys and a unilateral nonfunctioning kidney are contraindications to splachnicectomy. Evidence of moderate damage from previous pyelonephritis is no longer considered a contraindication, since some patients with this condition have shown satisfactory improvement in the blood-pressure level. Further studies are now being carried out, but a preliminary survey fails to show

any correlation between the amount of damage from pyelitis and the postoperative blood-pressure level.

Decision regarding operability never rests on the maximum water concentration and urea clearance determinations alone. These findings are usually paralleled by the height of the blood nonprotein nitrogen. A nonprotein nitrogen above 45 mg per 100 cc when the patient has been taking adequate amounts of fluid is a definite contraindication to splachnicectomy. It is true that we have occasionally operated when the nonprotein nitrogen was above this level, but these patients have shown only temporary improvement, occasionally lasting for a year, or no improvement. Even a nonprotein nitrogen above 42 mg per 100 cc suggests permanent renal damage and gives a poorer prognosis. We prefer the nonprotein nitrogen to be below 40 mg per 100 cc.

Severe renal complications, as evidenced by a measurable amount of albumin in the urine and red cells or occasional casts in the sediment, do not militate against a good surgical result. A significant number of patients have had gross hematuria, even to the extent of so-called "renal apoplexy", in the majority of cases these signs of renal damage have disappeared after splachnicectomy.

A differential diagnosis between chronic glomerulonephritis and renal disease secondary to hypertension must be made, since the former is not amenable to operation. The clinical and laboratory findings may be identical in the two diseases, and the differential diagnosis may depend on the history. Usually, in chronic glomerulonephritis, there is a history of an acute episode of nephritis, often with generalized edema and albuminuria with a normal blood pressure. In some cases only the repeated finding of albumin in the urine before hypertension is manifest makes possible the diagnosis of a primary nephritis and thus rules out splachnicectomy. Conversely, in early hypertension, the urine is normal.

The so-called "hypertensive toxemia of pregnancy," unless there is a definite history of a preceding nephritis, is not a contraindication for splachnicectomy. Many patients give a history of an elevated blood pressure during pregnancy with a return to normal or at least a marked reduction after delivery, only to have the pressure rise still higher in a subsequent pregnancy and remain definitely elevated after its termination. In most of these cases the hypertension has tended to progress. Some of our most brilliant results following splachnicectomy have occurred in patients in whom pregnancy appeared to be the precipitating etiologic factor.

The question of whether a splachnicectomy should be performed on a patient with a definite history of a cerebrovascular accident cannot be answered arbitrarily. Each case must be judged individually. Certain general rules have been

adopted, however. A patient under fifty years of age who has completely recovered from one or more cerebrovascular accidents does not present an unusually high surgical risk. If other findings are favorable, we recommend operation and with a definite hope of preventing another stroke. The presence of severe brain damage as evidenced by aphasia or hemiplegia, is certainly a contraindication to this operation.

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The blood pressure, both systolic and diastolic, was significantly reduced five to twelve years after splanchnicectomy in 81.3 per cent of the patients still living. There had been no change from pre-operative levels in 12.7 per cent. Over the course of years only 6 per cent had an increase in blood pressure. Many of the patients who died (49 per cent had malignant hypertension) during the post-operative period of five to twelve years had had significant reductions in their blood pressure, but regardless of the addition of these cases to those not showing improvement, there was a worth-while reduction of blood pressure in 46.7 per cent of the entire series.

We consider a blood pressure of 140 systolic, 90 diastolic, normal for patients under forty, and one of 150 systolic, 95 diastolic, normal for those over forty. With these criteria, 20.3 per cent of patients have maintained normal pressure for five to twelve years.

A reduction in blood pressure of over 80 systolic, 25 diastolic, although not to normal, is considered a marked improvement. Such a reduction was maintained for the entire postoperative period of five to twelve years in 26 per cent of cases. A significant improvement (a reduction of more than 40 systolic, 15 diastolic) was maintained in 35 per cent.

Considering the patients whose blood pressure has been reduced to normal and those with marked and significant reductions, there was an over-all improvement in blood pressure in 81.3 per cent of the living patients, and the improvement has been maintained to date, that is, five to twelve years after operation.

The funduscopic findings in cases that before operation showed angiospastic retinitis with or without hemorrhages or exudates now show absence of angiospasm, hemorrhages or exudates in 82 per cent. Papilledema disappeared, and in the 21 patients with malignant hypertension who are still living five to twelve years after splanchnicectomy it has not returned.

The cardiac status showed a similar improvement, which was maintained over the long period of post-operative study, patients with marked enlargement of the heart preoperatively showed a significant reduction in 52 per cent. Symptomatic improvement, evidenced by relief of anginal pain, palpitation and shortness of breath, was striking. Some patients who had had frequent attacks of angina pectoris had been completely relieved, and there had been no return of painful attacks under either excitement or exercise for the several years of postoperative study. In a significant number of patients with abnormal electrocardiograms before operation, including those with angina pectoris, the electrocardiogram returned to normal.

The renal function following splanchnicectomy has shown definite improvement, both in water-concentrating ability and urea clearance. Recent

studies have not been completed, but in an earlier study, 45 per cent showed a return of urea clearance to normal and 44 per cent had improvement in water concentration. Red cells and albumin have disappeared from the urinary sediment.

It should be borne in mind that practically all our hypertensive patients had had modern medical treatment, sometimes for years and under the direction of able internists, before being referred to us for splanchnicectomy. Such medical treatment had failed to prevent further progress of the disease, as evidenced by persistent or increasing blood pressure, continuing of impairment of cardiac or renal functions, advancing eye changes, cerebral accidents and intensified symptoms. Therefore, the improvement noted after splanchnicectomy can be directly attributed to the operation.

Improvement in life expectancy is best judged by the results in cases of malignant hypertension. In the series of Keith, Wagener and Barker¹⁰ there was a mortality of 78 per cent at the end of the first year, compared to our mortality of 36 per cent after splanchnicectomy. At the end of two years under medical treatment there was a mortality of 88 per cent, compared to a mortality of 50 per cent in those treated surgically. At the end of five years only of 146 patients treated medically was still living whereas 35 per cent were living after splanchnicectomy. Of special significance is the fact that 19 per cent of our patients with preoperative malignant hypertension are still living five to thirteen years after bilateral supradiaphragmatic splanchnicectomy.

The ability to resume a gainful occupation is of vital importance to a large number of incapacitated hypertensive patients. The frequently given advice to "slow down" and "lessen or stop working" is economically impossible for a vast number of patients. Often this advice is coupled with the phrase "stop worrying." Just how a man who needs to support his family and is told that he must stop work can help from worrying is not explained. The ability of the hypertensive patient to resume work after splanchnicectomy is one of the most gratifying results. In one of our special follow-up studies extending for a postoperative period of seven years, 55.5 per cent of patients had completely recovered from their incapacitation and had been able to return to their former occupations. Many others were so improved that they were again employed, making a total improvement from incapacitation of 81.3 per cent. The majority were able to resume work only a few weeks after the bilateral supradiaphragmatic splanchnicectomy.

Perhaps as severe a test of the efficacy of splanchnicectomy for hypertension as can be made is that of pregnancy some time after the operation. Pregnancy often appears to be the instigating factor in the development of hypertension in apparently healthy women. It is well known that pregnancy frequently accelerates the hypertensive process when

the disease is already present, so much so in some cases that a therapeutic abortion is indicated to save the mother. We have a number of patients who had had severe hypertension, in one with a systolic pressure of over 300 in whom following a bilateral supradiaphragmatic splanchnicectomy the pressure dropped to and remained normal, a subsequent pregnancy was carried to completion without incident. These pregnancies occurred one to several years after the splanchnicectomy. In none did the blood pressure rise above normal either during or after the pregnancy. All patients were free of hypertensive symptoms, and none showed any evidence of cardiac impairment or abnormal renal function.

The following case reports are given to illustrate the results obtained by bilateral supradiaphragmatic

returned with incapacitating severity, and nausea and vomiting were associated. She had noted blurring of vision for 1 month. She had been confined to bed for the previous 8 months because of the severity of the symptoms.

Physical examination revealed a severe neuroretinitis with early papilledema, flame-shaped hemorrhages and cotton-wool patches, the retinal arteries showed marked variation in caliber, with localized angiospasm and arteriovenous compression. Both lung fields were clear. The heart was not enlarged. A soft systolic murmur was heard over the precordium. Neither kidney was palpated. There was no peripheral edema. The blood pressure averaged 280/190 in both arms.

An electrocardiogram showed inverted T waves in Leads 2 and 3. Urinalysis revealed a proteinuria of 0.12 per cent, and a moderate number of red cells and casts in the sediment. The maximum specific gravity on a 38-hour concentration test was 1.033. Urea clearance was 87 per cent. A phenol-sulfonephthalein test showed 24 per cent excretion of the dye in 15 minutes. There was no anemia, and the blood serologic findings were negative.

A bilateral supradiaphragmatic splanchnicectomy was per-

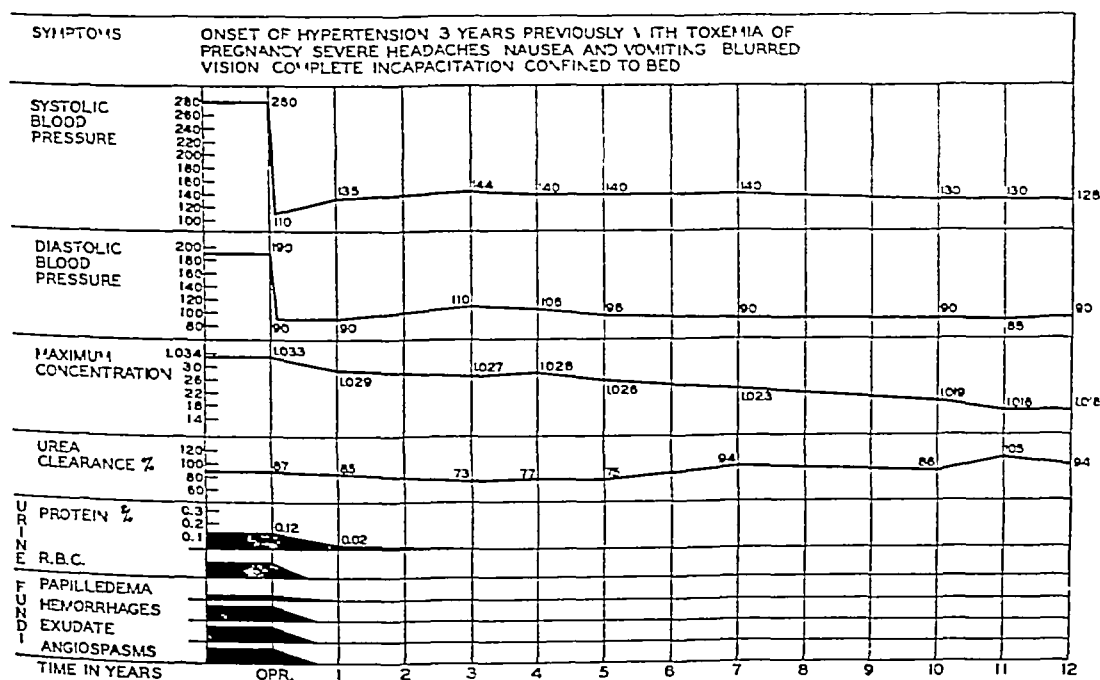


FIGURE 1 Summary of Data in Case 1

matic splanchnicectomy in many patients with severe hypertension. The first is a case of typical malignant hypertension, the second a case of hypertension with severe angina, and the third a case of pregnancy following splanchnicectomy.

Case 1 (Fig 1) Malignant hypertension. V E, a 22-year-old married woman, entered the hospital on June 16, 1934, complaining of severe headaches. An elevated blood pressure had been discovered during her first pregnancy 3 years previously, when she had complained of swollen ankles, unbearable headaches and blurred vision. The systolic blood pressure reached 250 with the toxemia of pregnancy, labor was induced during the 8th month, and a living infant was obtained. One year later the child died, and the patient immediately began to have episodes of severe precordial pain with associated numbness in the left arm. The headaches

formed on June 22. The postoperative course was uneventful and the patient was discharged in 14 days.

Follow-up study 2 months after operation disclosed a blood pressure of 145/90. The patient was completely asymptomatic. The maximum specific gravity was 1.028. The phenol-sulfonephthalein test showed 50 per cent excretion of the dye in 15 minutes. The proteinuria was 0.02 per cent. Examination of the fundus revealed that the hemorrhages and exudates had completely disappeared and that the arteries were practically normal, both optic disks were well outlined.

One year after operation the blood pressure was 135/90, and the patient was still completely asymptomatic. The ocular fundi were normal. The maximum specific gravity was 1.029, and the urea clearance was 85 per cent. The phenol-sulfonephthalein test showed 37 per cent excretion of the dye in 15 minutes. There was a proteinuria of 0.02 per cent.

Three years after operation the blood pressure was 144/110. The patient complained of a recurrence of the episodes of pre-

cordial pain. An electrocardiogram showed inverted T waves in Leads 2 and 3. A left superior cervical ganglionectomy was performed. The ocular fundi were normal. There was no proteinuria. The maximum specific gravity was 1.027, and the urea clearance was 73 per cent.

A year later the blood pressure was 140/106, and the patient was asymptomatic, with normal fundi. The specific gravity was 1.028, and the urea clearance was 77 per cent. There was no proteinuria.

Five years after operation the blood pressure was 140/96. The patient was still asymptomatic, with normal fundi. An electrocardiogram was within normal limits, with upright T waves. A teleroentgenogram revealed the heart to be of normal size. The specific gravity was 1.026, and the urea clearance was 75 per cent. There was no proteinuria.

Two years later examination revealed that the blood pressure was still 140/90, the patient was asymptomatic. There was a slight sclerosis of the retinal arterioles. There was no proteinuria. The maximum specific gravity on an 18-hour concentration test was 1.023 (previous follow-up tests had all been performed on a concentration of 36 hours). The urea clearance was 94 per cent.

Ten years after operation the blood pressure was 130/90, and the patient was asymptomatic. An electrocardiogram was normal, and the heart size was unchanged on a teleroentgenogram. The ocular fundi showed a slight sclerosis of the arterioles. The maximum specific gravity on an 18-hour concentration test was 1.019. The urea clearance was 86 per cent.

Eleven years after operation the blood pressure was 130/88, and the patient had no symptoms. There was a slight sclerosis of the retinal arterioles. An electrocardiogram was normal, as was the heart size. The maximum specific gravity on an 18-hour concentration test was 1.016, and the urea clearance was 105 per cent.

Twelve years after operation the blood pressure was 128/90, and the patient was still asymptomatic. There was a mild sclerosis of the retinal arterioles. An electrocardiogram and the heart size were normal. The maximum specific gravity was 1.016 on an 18-hour concentration test. The urea clearance was 94 per cent.

CASE 2 Hypertension with severe angina pectoris. M S, a 40-year-old housewife, entered the hospital on September 2, 1941, complaining of episodes of excruciating pain across the upper anterior chest that were consistently related to exertion and disappeared after 5 to 15 minutes of rest. She had first been discovered to have high blood pressure 10 years previously. She had had two to six episodes of severe substernal pain daily for the previous month.

Physical examination revealed a moderate sclerosis, localized angiospasm and arteriovenous nicking but no hemorrhages or papilledema. Both lung fields were clear. The heart was not enlarged, a definite presystolic gallop was heard at the apex, the aortic second sound was snapping. Neither kidney was palpated. There was no peripheral edema. The blood pressure averaged 230/150 in both arms.

An electrocardiogram revealed deeply inverted T waves in Leads 1 and 2 and in the chest leads, suggesting a recent anterior myocardial infarction. The heart size was normal on a teleroentgenogram. Urinalysis was negative. The maximum specific gravity was 1.021. The urea clearance was 68 per cent. The blood nonprotein nitrogen was 32 mg per 100 cc.

The patient continued to have at least two anginal seizures daily while at rest in bed. On September 9 the T waves were much less inverted than those in the previous electrocardiogram. The blood pressure remained at 220/140. On September 18, a protracted episode of severe substernal pain required morphine for relief. On the next day the electrocardiogram showed prominent Q waves in Leads 2 and 3 and evidences of a fresh posterior myocardial infarction. Anginal seizures continued while the patient was at rest in bed. Serial electrocardiograms showed evidences of healing of the infarct. The blood pressure remained high.

Because of the persistent anginal seizures and high blood pressure, bilateral splanchnicectomy was performed on October 17. Although two recent myocardial infarcts had occurred, the postoperative course was uneventful. The patient was discharged on November 5, she did not have a single anginal seizure following operation.

Follow-up examination 5 years after operation disclosed

complete relief from the anginal seizures, there had been no subsequent coronary occlusion. The blood pressure was 164/114. No gallop rhythm was apparent. An electrocardiogram showed prominent Q waves in Leads 2 and 3. The heart size was normal on a teleroentgenogram. The maximum specific gravity of the urine was 1.021.

CASE 3 Pregnancy following splanchnicectomy. G T, a 23-year-old woman, was admitted to the hospital on April 16, 1938. She had first learned that she had an elevated blood pressure 2 years previously, when she had consulted a physician because of occipital headaches. The headaches increased in severity and frequency until admission. There were no other complaints.

Physical examination revealed marked attenuation of the retinal arterioles and occasional localized angiospasm; there was a cotton-wool patch temporal to the disk of the left eye, both disks were well outlined. Both lung fields were entirely clear, and the heart showed nothing unusual. Neither kidney was palpated, and there was no peripheral edema. The blood pressure averaged 230/145 in both arms.

An electrocardiogram was within normal limits. A teleroentgenogram revealed a heart of normal size. Urinalysis was negative for proteinuria. The blood nonprotein nitrogen was 17.2 mg per 100 cc. The maximum specific gravity on a 38-hour concentration test was 1.023. The urea clearance was 89 per cent of normal. There was no anemia, and the blood serologic findings were negative.

Bilateral splanchnicectomy was performed on April 20. The patient was discharged on the 12th postoperative day.

Follow-up examination 2 years after operation revealed complete relief from preoperative headaches, the patient was working full time as a bookkeeper and had no complaints. The ocular fundi were normal. The blood pressure was 126/82. An electrocardiogram was within normal limits, and the heart was normal on a teleroentgenogram. The maximum specific gravity was normal at 1.026 on an 18-hour concentration test. The urea clearance was 93 per cent.

Five years after operation the patient completed a full term pregnancy, a normal infant being delivered. The blood pressure remained normal, and there was no albuminuria during the entire pregnancy.

Seven years after operation the blood pressure was 118/86, and the patient was completely asymptomatic. An electrocardiogram was normal, and the heart size normal on a teleroentgenogram. The maximum specific gravity was 1.025.

SUMMARY

The etiology of hypertension is considered, especially in its bearing on surgical treatment. A new classification of arterial hypertension is presented, based on the predominant pathologic lesion.

Bilateral supradiaphragmatic splanchnicectomy, which includes excision of the greater, lesser and least splanchnic nerves, is considered the procedure of choice. The operation has been performed at the University of Michigan Hospital on over 1500 patients. The results of studies over a postoperative period of one to twelve years are given. Significant improvement in reduction of blood pressure, improvement in ocular, renal and cardiac status, alleviation of symptoms, relief of incapacitation and probable prolongation of life are reported.

Three typical case reports or the relief afforded by bilateral splanchnicectomy are presented.

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REFERENCES

1. Page, I. H. Classification of hypertension. *J. Indiana M. A.* 32: 562, 1939.
2. Goldblatt, H., Lynch, J., Hanzal, R. F. and Summerville, W. W. Studies on experimental hypertension. I. Production of persistent elevation of systolic blood pressure by means of renal ischemia. *J. Exper. Med.* 59: 347-379, 1934.

- 3 Foa, P. P., Woods, W. W., Peet, M. M., and Foa, N. L. Effective renal blood flow, glomerular filtration rate and tubular excretory mass in arterial hypertension. II. Effect of supradiaphragmatic splanchnicectomy with lower dorsal sympathetic ganglionectomy. *Arch. Int. Med.* 71:357-369, 1943
- 4 Adson, A. W. Tratamiento quirúrgico de la hipertensión esencial por medio de la resección de los nervios espláncicos y del primero y segundo ganglios simpáticos lumbares. *Rev. mex. de cir., ginec. y cancer* 6:229-246, 1938
- 5 Craig, W. M. Essential hypertension: selection of cases and results obtained by subdiaphragmatic extensive sympathectomy. *Surgery* 4:502-509, 1938
- 6 Peet, M. M. Surgical treatment of hypertension. *J. internat. de chir.* 5:1-50, 1940
- 7 Smithwick, R. H. Technique for splanchnic resection for hypertension: preliminary report. *Surgery* 7:1-8, 1940
- 8 Grimson, K. S. Total thoracic and partial to total lumbar sympathectomy and celiac ganglionectomy in treatment of hypertension. *Ann. Surg.* 114:753-775, 1941
- 9 Peet, M. M., and Isberg, E. M. Surgical treatment of arterial hypertension. *J. A. M. A.* 130:467-473, 1946
- 10 Keith, N. M., Wagener, H. P., and Barker, N. W. Some different types of essential hypertension: their course and prognosis. *Am. J. M. Sc.* 197:332-343, 1939

PENICILLIN IN THE TREATMENT OF GONORRHEA IN WOMEN

Results of Treatment as Reported by Twelve Co-operating Venereal-Disease Clinics in Massachusetts during 1945

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THE application of penicillin seems to be the outstanding advance to date in the therapy of gonorrhea, the most frequent of all venereal infections. The results of treatment in both sexes, with or without complications, are so striking that all other forms of therapy now seem antiquated. This is not to say, however, that penicillin is a "miracle drug" that relieves the physician and follow-up workers of any further responsibility once a patient has received a course of treatment.

Critical analysis of the data available shows that one may come to some tentative conclusions. There are enough failures of treatment to necessitate careful repeated follow-up examinations, which should include at least four or five cultures and smears for the gonococcus. The optimum treatment schedule has yet to be worked out, but the underlying principles seem to aim at producing penicillin blood levels high enough to accomplish the desired results over a relatively short period rather than lower blood levels for a prolonged period. The rationale of this is twofold: the goal is to develop an ambulatory treatment that can be completed at one clinic session, and experience seems to show that dosage schedules that achieve these high penicillin blood levels produce a larger percentage of satisfactory results. Because of the well known repressive action of the drug on the spirochetes of syphilis, blood serologic tests should be taken six weeks after treatment and should be repeated in three months.

This paper represents an analysis of the data collected from twelve clinics that co-operate with the Division of Venereal Diseases, Massachusetts Department of Public Health. The study includes female patients with gonorrhea who were treated with aqueous solutions of sodium penicillin and

whose cases were reported to the division on special "Penicillin Study" forms from September, 1944, to January, 1946.

Many of the numerous papers written on the use of penicillin in the treatment of gonorrhea have been reports of the results of research in this field. The data of one of the co-operating clinics in Massachusetts, which is engaged in active research, are not included in this study. We are interested in examining the results of various treatment schedules as applied by a representative group of clinicians under widely differing circumstances. It is as a picture of what penicillin may be expected to accom-

TABLE 1 Results of Penicillin Treatment of Gonorrhea in Women

TOTAL DOSAGE OF PENICILLIN	TOTAL NO OF CASES	CURES		FAILURES	
		NO OF CASES	PERCENTAGE	NO OF CASES	PERCENTAGE
500,000	135	119	88	16	12
100,000	41	41	100	0	0
200,000	44	40	91	4	9
300,000 or more	14	12	86	2	14
Totals	234	212		22	
Averages			91		9

plish in a representative cross section of venereal-disease clinics that this paper is presented. Studies of this kind will eventually establish a sound rationale for routine treatment schedules that are applicable on a large scale for the therapy of gonorrhea in women.

Table 1 presents a summary of the results of treatment under the various dosage schedules employed in this series. Thirty-two cases reported on the study sheets were not followed after treatment and are not included in the table. Two hundred and thirty-four courses of treatment were given to

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200 patients with either proved or suspected gonorrhea. Those treated on suspicion without any particular clinical or laboratory evidence of gonorrhea were women who had been named as sources of infection by men with gonorrhea, in most cases these were military contacts.

The largest group of patients in the series received 100,000 units of penicillin. In all but 6 of these patients, who were treated according to the schedule of 20,000 units every two hours for five injections, the results were satisfactory, a percentage of 90 (Table 2). When penicillin first became available

of this case report disclosed that the patient was treated on suspicion on June 14, 1945. On follow-up study on June 20 and July 11 smears and cultures were negative. On August 8, two months after treatment, there was a positive culture, probably owing to reinfection rather than to failure of treatment. The patient was again treated with a course of 100,000 units (20,000 units every two hours for five doses), but the culture remained positive. A third course of 50,000 units every two hours for three injections finally resulted in a cure.

There were three failures in the group of 19

TABLE 2 *Results of Treatment with 100,000 Units of Penicillin according to Interval between Injections*

No. of Injections	Two Hours Between Injections		Three Hours Between Injections		Four Hours Between Injections		Totals	
	Cures	Failures	Cures	Failures	Cures	Failures	Cures	Failures
3	3 (75%)	1 (25%)	—	1 (100%)	2 (67%)	1 (33%)	5 (62%)	3 (37%)
4	1 (100%)	—	—	—	—	—	1 (100%)	—
5	112 (90%)	13 (10%)	1 (100%)	—	—	—	113 (90%)	13 (10%)
Totals	116 (89%)	14 (11%)	1 (50%)	1 (50%)	2 (67%)	1 (33%)	119 (88%)	16 (12%)

for distribution to the co-operating clinics, this was the schedule recommended.

Forty-one patients were treated with 150,000 units of penicillin. All of these were given 50,000 units every two hours for three doses. The results were 100 per cent satisfactory. This schedule seemed to give the best results, which is surprising in view of the fact that the 44 cases treated with 200,000 units showed failures in 4, a rate of 9 per cent.

Table 3 presents the details of the various treatment schedules employed with a total dosage of 200,000 units. Eight patients were given three

patients who received 50,000 units every two hours for four injections — a total dose of 200,000 units. Analysis of the individual case reports shows that two of these failures occurred in a patient who either was resistant to penicillin or became reinfected repeatedly, or both, the failures occurred on the second and third courses of treatment. The former may well have been caused by reinfection following the first course of treatment with 100,000 units. The patient eventually developed pelvic inflammatory disease and received a fourth course of treatment, totaling 600,000 units, in the hospital.

TABLE 3 *Results of Treatment with 200,000 Units of Penicillin according to Interval between Injections*

No. of Injections	Two Hours Between Injections		Three Hours Between Injections		Four Hours Between Injections		Totals	
	Cures	Failures	Cures	Failures	Cures	Failures	Cures	Failures
2	—	—	—	—	7 (88%)	1 (12%)	7 (87%)	1 (12%)
3	8 (100%)	—	—	—	—	—	8 (100%)	—
4	16 (84%)	3 (16%)	—	—	—	—	16 (84%)	3 (16%)
5	4 (100%)	—	—	—	—	—	4 (100%)	—
More than 6	1 (100%)	—	4 (100%)	—	—	—	5 (100%)	—
Totals	29 (91%)	3 (9%)	4 (100%)	—	7 (88%)	1 (12%)	40 (91%)	4 (9%)

injections of 66,666 units each at two-hour intervals. All were cured. This standard schedule was introduced by the Department of Public Health during the latter part of 1945. The excellent results in the small group recorded sustain the judgment in recommending the change, although the group is too small as yet to have statistical significance.

Further study of Table 3 shows that there were 4 cases of failure among patients receiving 200,000 units. One of these patients received two injections of 100,000 units each, four hours apart. Analysis

Subsequently, four consecutive smears and cultures were negative. Two months after treatment she returned to the clinic with positive smears and cultures. Although she denied re-exposure, it is difficult to accept this case as one of failure in the fourth course of treatment. The third treatment failure occurred in a woman who returned with pelvic inflammatory disease a month after the course of therapy. There is nothing in the report to indicate that this case could not have been the result of reinfection rather than a failure of treatment.

A total of 14 patients received 300,000 units or more, with failure in 2 (Table 4), one of which was the doubtful failure mentioned above. The results in this small group were 86 per cent successful. If

more appears to be adequate except for the unusual case caused by a resistant strain.

Table 6 demonstrates a definite decline in the trend of curability as the duration of infection

TABLE 4 Results of Treatment with 300,000 or More Units of Penicillin according to Interval between Injections

No. of Injections	TWO HOURS BETWEEN INJECTIONS		THREE HOURS BETWEEN INJECTIONS		TOTALS	
	CURES	FAILURES	CURES	FAILURES	CURES	FAILURES
4	2 (100%)	—	—	—	2 (100%)	—
More than 6	6 (86%)	1 (14%)	4 (50%)	1 (20%)	10 (83%)	2 (17%)
Totals	8 (89%)	1 (11%)	4 (50%)	1 (20%)	12 (86%)	2 (14%)

the doubtful failure is reclassified as a case of reinfection, the rate of cure becomes 93 per cent.

Table 5 presents the results of treatment in relation to the number of courses for each patient and

lengthens. Twenty-five patients with infections lasting up to fourteen days were cured, patients whose infection had persisted for fifteen to twenty-eight days showed 97 per cent cures. In the chronic

TABLE 5 Results of Treatment according to Total Dosage and Courses of Penicillin

TOTAL DOSAGE	FIRST COURSE		SECOND COURSE		THIRD COURSE		FOURTH COURSE		TOTALS	
	CURES	FAILURES	CURES	FAILURES	CURES	FAILURES	CURES	FAILURES	CURES	FAILURES
100,000	110 (89%)	13 (11%)	7 (70%)	3 (30%)	2 (100%)	—	—	—	119 (88%)	16 (12%)
150,000	35 (100%)	—	5 (100%)	—	1 (100%)	—	—	—	41 (100%)	—
200,000	35 (97%)	1 (3%)	4 (67%)	2 (33%)	1 (50%)	1 (50%)	—	—	40 (91%)	4 (9%)
300,000 or more	6 (100%)	—	—	1 (100%)	5 (100%)	—	1 (50%)	1 (50%)	12 (86%)	2 (14%)
Totals	186 (93%)	14 (7%)	16 (73%)	6 (27%)	9 (90%)	1 (10%)	1 (50%)	1 (50%)	212 (91%)	22 (9%)

to the total dosage used. The first course of treatment gave satisfactory results in 93 per cent of cases regardless of the total dosage used. The patients receiving 100,000 units made the poorest

cases and those in which the duration of infection was unknown, the cures were 92 and 85 per cent respectively. Recent work on the mode of action of penicillin indicates that bacteria are most vulnerable to the action of penicillin during the period of greatest reproductive activity. This may explain the difference in the response of acute gonorrhea to penicillin therapy as compared with that of the chronic condition. In addition, the greater activity of the host tissues in the characteristic reaction of an acute inflammation must be considered.

Table 7 presents the interesting observation that

TABLE 6 Results of Treatment according to Duration of Infection

DURATION OF INFECTION	CURES	FAILURES
0-14 days	25 (100%)	—
15-28	30 (97%)	1 (3%)
29 or more	76 (92%)	7 (8%)
Unknown	81 (85%)	14 (15%)
Totals	212 (91%)	22 (9%)

showing, with cure in only 89 per cent. If the doubtful failure referred to above is regarded as a case of reinfection, the treatment in the groups in which 150,000 units or more were employed was 99 per cent successful.

The conclusion may be drawn from this series that 100,000 units of penicillin does not constitute an adequate dose for achieving uniformly reliable results in the treatment of gonorrhea in women. Any dosage schedule employing 150,000 units or

TABLE 7 Results of Treatment according to Complications

TYPE OF GONORRHEA	RESULT	
	CURES	FAILURES
Uncomplicated	199 (91%)	21 (9%)
Complicated	13 (93%)	1 (7%)
Totals	212 (91%)	22 (9%)

the percentage of cured cases was higher in the group with complications than in that without complications. The difference, however, is not statistically significant. In general, the patients with

complications received larger doses than those with uncomplicated gonorrhea. Table 7 shows, however, that penicillin is equally effective in the treatment of gonorrhea with or without complications.

* * *

This study was based on the tabulation of information sent in by twelve co-operating clinics in Massachusetts regarding cases of gonorrhea in

women who had been treated with varying courses of intramuscular injections of an aqueous solution of penicillin. Two hundred and thirty-four courses of treatment were given in 200 cases. The best results were obtained by the use of 150,000 units or more of penicillin divided into three equal doses spaced two hours apart.

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MEDICAL PROGRESS

SYPHILIS (Concluded)

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REACTIONS TO TREATMENT

A word of caution has been given by Leifer⁵⁶ regarding the continuance of arsenotherapy in patients experiencing the reaction known as erythema of the ninth day. This is an entirely distinct disturbance from the systemic Herxheimer reaction, which occurs only after the initial dose of arsenic or, rarely, after the second injection. Erythema of the ninth day may occur any time within the first three weeks of arsenotherapy, and Leifer considers it a probable manifestation of sensitivity to arsenic. An erythematous eruption may or may not be present, but fever always occurs and there may be acute hepatitis. It was often assumed that arsenotherapy could safely be resumed from one to six months after erythema of the ninth day, depending on the severity of the reaction. Leifer reports 14 cases in which the reinstitution of arsenical treatment after erythema of the ninth day was followed by a severe parenchymatous injury in the form of jaundice and agranulocytosis, with or without nephritis. Arsenotherapy had been rather promptly resumed in all these patients, 12 of whom subsequently received an intensive course of penicillin without untoward reactions.

For a considerable period after the introduction of oxophenarsine hydrochloride (Mapharsen), it was maintained that the drug caused no serious reactions and comparatively few untoward effects of any kind. As it was more widely used, however, reports of damaging effects gradually appeared in the literature. Two more cases of acute agranulocytosis, one with coexisting toxic hepatitis, have been attributed to Mapharsen therapy for syphilis.⁵⁷ Colloido-

clastic shock has rarely been reported from the use of Mapharsen, but another report of a case of this reaction has appeared.⁵⁸

It has often been pointed out that post-arsphenamine jaundice is clinically indistinguishable from infectious hepatitis. A particularly interesting example of this problem was reported in a clinical observation of syphilitic patients treated in England during the period 1941-1944.⁵⁹ Fifty per cent of the patients studied developed jaundice, the majority on about the hundredth day after the first injection. Following routine sterilization of syringes before and after each injection, the incidence of hepatitis was reduced from 50 to 10 per cent. This indicates that post-arsphenamine jaundice was spread by contaminated syringes. It could just as easily be deduced that all the patients had infectious hepatitis of the epidemic type that was transmitted by the syringes.

An example of the dangers of massive drip arsenotherapy may be found in the report of 2 additional cases of encephalopathy.⁶⁰ The first patient received 240 mg of Mapharsen over a period of eight hours, none was given thereafter. Hepatitis and toxic encephalopathy followed. The patient died eight days later. The other patient received a total dosage of 720 mg of Mapharsen in three days. A toxic erythema developed, followed by stupor and convulsive seizures. Death occurred four days after the termination of arsenotherapy. In both cases excellent care and the best forms of treatment were used.

A systemic treatment for arsenic poisoning has appeared under the name BAL or British antilewisite (2,3-dimercaptopropanol). This compound was developed during the war as an antidote to arsenical blister gases. The compound was subse-

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quently found to be effective also in the systemic treatment of severe arsenic poisoning. Eagle⁶¹ reported that BAL has been used in more than 200 cases in various types of arsenic poisoning with results indicating that the danger of some complications may be markedly reduced by its early administration in adequate dosage. Urinary excretion of arsenic is increased for two to four hours after therapy. The drug is injected intramuscularly in oil, 25 mg per kilogram of body weight being given at each dose. Four doses are given the first two days and decreasing amounts thereafter for twelve days. In grave complications larger amounts may be used for longer periods. Of 55 patients with hemorrhagic encephalitis, 44 recovered in one to seven days. Among 51 patients with exfoliative arsenical dermatitis, 80 per cent improved within three days and recovered almost completely in thirteen days. Ten of 11 patients with agranulocytosis showed approximately normal white-cell counts within seven days. Aplastic anemia was not affected. Post-arsphenamine jaundice was cured in only 5 of 14 patients. Gluteal abscesses or cellulitis may occur with the use of this drug.

PENICILLIN

During the past year the use of penicillin in the treatment of syphilis has been widely extended. It should be emphasized at the outset, however, that the use of this drug in the treatment of syphilis should still be regarded as experimental and that the drug should not be employed without some routine chemotherapy, in conjunction with and subsequent to the penicillin. As pointed out below, the effectiveness of penicillin for the treatment of syphilis seems to be distinctly reduced, and increased dosage schedules have been advocated. This situation is being remedied, but it serves to illustrate how much has yet to be learned about the drug.

Experimental Research

The distribution of penicillin in the body after injection is not too difficult to determine in animals, but the fate of the drug is not entirely understood.⁶² It has been shown that penicillin is widely distributed through all the tissues and organs, with the exception of the nervous system. The rate of disappearance of penicillin from the blood does not seem to be influenced by biliary obstruction in rabbits, but its effect was greatly prolonged by renal obstruction. Although the major part of administered penicillin is lost in the urine and a lesser amount in bile and saliva, there remains a portion for which the fate remains unknown.

In vitro studies have shown that the action of penicillin is far greater on organisms undergoing rapid rate of growth and with increasing temperature.⁶³ At high temperatures the drug kills organisms that are not undergoing growth, this action would

otherwise require excessively high concentrations of the drug. Heightened effectiveness under increased temperatures explains the valuable effect of penicillin combined with hyperpyrexia in the treatment of neurosyphilis, as pointed out by clinical reports cited below.

Several variants of penicillin have been isolated in crystalline form. The comparative sensitivity of numerous bacterial strains to the different types of penicillin has been worked out.⁶⁴ Penicillin G is the one that seems to have the greatest effect on *T. pallidum*,⁶⁵ as demonstrated by the accelerated disappearance of surface organisms from dark-field-positive lesions. The proportions of penicillin fractions included in various commercial penicillins vary. All are apparently effective in the treatment of gonorrhea, and each of the various fractions appears to have enough effect on *T. pallidum* to mask syphilis when used in the treatment of gonorrhea.

It is believed that the action of penicillin interferes with bacterial metabolism in the early stages of growth.⁶⁶ Spirochetes isolated from patients receiving penicillin treatment were observed to become elongated. After being repeatedly passed through mediums containing penicillin, a laboratory strain of *T. pallidum* did not appear to have developed an increased tolerance to the drug.⁶⁷ Elongation of the spirochete was observed with electron-microscope studies of these cultures, and the organisms had also lost their flagella. This lengthening of the organism seemed to indicate an inhibition of cellular division. Although spirochetes have been repeatedly demonstrated to become resistant to arsenicals if therapy is not correctly carried out, there is some question whether penicillin resistance actually occurs. It is stated that such resistance may be an inherited characteristic originating through mutation, its origin being independent of penicillin treatment.⁶⁸ If initial doses of the drug are high and it is continued vigorously until the infection has been eliminated, resistance should certainly not appear. Acquired resistance to penicillin has been produced in some organisms in vitro although the mechanism is unknown.⁶⁹ The development of penicillin resistance in man has been unimportant, but the general problem of penicillin resistance of *T. pallidum* remains unsolved. In a case report of early syphilis resistant to treatment with penicillin, 2,400,000 units were given over a period of five days.⁶⁹ The chancre did not heal, although the serologic test for syphilis became negative after several weeks. The test subsequently became positive, and secondary lesions appeared. Retreatment consisted of only 600,000 units of penicillin in conjunction with eight hours of fever therapy, the response was excellent. This seems highly questionable as actual evidence of penicillin resistance. The correct dosage and time-dose relation of penicillin therapy are not definitely established. It is known that prolongation of administration has decided advantages even with

relatively lower dosage. The short period (five days) during which treatment was given could thus be the explanation for failure in the case reported. In vivo studies suggest that the maintenance of the minimal inhibitory concentration will result in remission of the syphilitic disease.⁶⁸ The minimal effective blood serum level of penicillin is not yet established, but it has been assumed that a serum level of 0.078 units per cubic centimeter must be maintained. Relapse should be prevented by a sufficiently prolonged period of maintenance of effective serum levels of penicillin. Higher concentrations apparently serve no useful purpose. Experimental work of this type backs up clinical experience of the value of prolongation of the duration of treatment.

Methods of Administration

Attempts to provide more prolonged effective blood levels of penicillin are being continued, but no outstanding advance has been reported during the past year. Slower absorption of penicillin from the site of injection by its incorporation in oil and wax is currently undergoing wide usage. Methods of slowing the rate of excretion have not proved satisfactory for routine employment. For all acute infections of any severity and for syphilis, the oil and wax vehicle is so far considered inferior to more rapidly diffusible diluents.

The oral administration of penicillin continues to receive a good deal of attention. Four to five times the intramuscular dose must be administered orally to obtain serum levels of comparative effectiveness. It has been shown that oral therapy with penicillin is effective in gonorrhea⁷⁰ and in other infections in which low dosages of parenteral penicillin have proved adequate.⁷¹⁻⁷⁴ So far as is now known, it should be unmistakably stressed that the oral administration of penicillin in the treatment of syphilis has not yet been shown to be satisfactory.

The so-called "Romansky formula"^{75, 76} for penicillin in beeswax and peanut oil has been shown to maintain effective blood levels of penicillin for about twenty-four hours in some patients, it continues to be excreted in the urine for approximately three days. This method of penicillin therapy is reported as adequate for most situations but not for overwhelming infections. An average dose of 300,000 units is required. Subcutaneous administration of this preparation has also been employed with satisfactory results.⁷⁷ In the treatment of syphilis several daily doses rather than a single injection seem to be required for satisfactory effect.⁷⁸ Aluminum and penicillin mixtures have also been used,⁷⁹⁻⁸¹ with results that deserve continued experimentation. Like the oral administration of penicillin, however, oil and wax mixtures cannot yet be recommended for use in the treatment of syphilis. No satisfactory outpatient plan of penicillin therapy for this disease has so far been established.

Penicillin in Early Syphilis

The danger of masking early syphilis during the treatment of gonorrhea with penicillin is of considerable magnitude. Since the advent of the sulfonamide drugs and penicillin, it is simpler than ever before for the general practitioner to treat gonorrhea. The symptoms of this disease may develop and the treatment may be completed with apparent cure several days before the primary lesion of syphilis normally appears. The comparatively small amount of penicillin necessary to cure gonorrhea is sufficient to abort temporarily the lesions of early syphilis for a considerable period. I have observed a case of early syphilis with a history of penicillin therapy for gonorrhea fourteen months prior to the appearance of clinical early syphilis. Exposure to venereal infection of any sort during the intervening period was consistently denied. Continued reports of this phenomenon have appeared in print, and one cannot be too careful in following patients with gonorrhea for some months after treatment.

Experimental work with small doses of penicillin comparable to those used in the treatment of gonorrhea has been carried out in rabbits inoculated with syphilis. It was the opinion of Magnuson and Eagle,⁸² who did this work, that an actual abortion of the infection, rather than suppression of the development of the primary lesion, took place. Many of the delayed lesions were so small that comparable lesions in man might not be detected, an apparently asymptomatic condition being thus produced. The authors believed that patients with gonorrhea should be followed clinically and serologically for four months or longer, this certainly seems to be a minimum period of observation. A sufficient number of case reports illustrating the danger of suppressing syphilis during gonorrhea therapy⁸³⁻⁸⁷ are available to indicate that this may become a public-health problem. Some authors believe that when there is evidence or suspicion of coexisting syphilis, penicillin therapy for gonorrhea should be withheld until a definite diagnosis of syphilis can be established or eliminated.

The frequency with which penicillin therapy for syphilis is accompanied by a Herxheimer reaction makes it possible to utilize this phenomenon as a possible clue to syphilis when penicillin is used in the treatment of other infections. It has been stated that the occurrence of chills or fever accompanying penicillin therapy for gonorrhea not obviously complicated by syphilis is strong presumptive evidence of the coexistence of syphilis.⁸⁸ There are exceptions to the rule, but it is at least a safe precaution to subject a patient displaying a febrile reaction to closer than usual scrutiny for a period of several months following penicillin treatment for gonorrhea.

Sufficient data are beginning to accumulate regarding the treatment of early syphilis with penicillin to establish a more adequate appraisal of the dosage required to achieve satisfactory results. Only comparatively immediate effects can be deduced, however, until the patients have been followed for periods up to at least twenty years. Pillsbury^{89, 90} reports follow-up examinations of 792 patients, six months or more after treatment with penicillin as given by the routine Army schedule. Tables are presented showing the incidence of relapse, the types of lesions, the results of serologic tests at various intervals, as well as a comparison of these penicillin-treated patients with the groups receiving prolonged courses of arsenicals and heavy metal, and the twenty-day intensive arsenobismuth plans of therapy. Pillsbury found that although penicillin therapy in early syphilis exhibits few toxic effects and the patient is rendered promptly noninfectious, with a low incidence of infectious relapses, this treatment compares unfavorably with arsenobismuth therapy in its achievement and maintenance of seronegativity. With a prompt diagnosis of syphilis the effectiveness of a single course of penicillin treatment is extremely high, 98.18 per cent of seronegative primary syphilis cases and 87.32 per cent of seropositive primary syphilis cases were considered satisfactory cures. Of the patients with secondary syphilis only 72.07 per cent became seronegative. Spinal-fluid examinations showed the incidence of progression to neurosyphilis to be extremely low as compared with those following arsphenamine and heavy-metal therapy. Penicillin, as a single therapeutic agent against syphilis, although it is remarkably effective, appears to deserve the assistance of some metallic therapy. Schoch and Alexander⁹¹ advocate the concurrent use of penicillin and Mapharsen. They have given 2,400,000 units of penicillin over a period of seven and a half days in conjunction with 40 mg of Mapharsen daily for eight days, an alternate program includes the same amount of penicillin with bismuth salicylate 0.2 gm in oil on alternate days for five injections. The results with both combinations show a definitely higher cure rate than with penicillin alone. These authors also advocate coincidental penicillin treatment of sexual partners, regardless of proof of infection, to prevent reinfections of the so-called "ping-pong type." Penicillin schedules employed by the United States Navy⁹² require 2,400,000 units for primary syphilis, whereas patients with secondary and latent cases receive 4,000,000 units. Therapeutic results were comparable to those of the preceding reports.⁹³ Others are in agreement that a dosage of 2,400,000 units is the minimal satisfactory amount of penicillin for early syphilis and that varying quantities of chemotherapy in conjunction with or subsequent to the penicillin are advisable.⁹⁴⁻¹⁰¹ There has been experimental work in animals to verify this opinion.¹⁰² The use of penicillin com-

bined with fever therapy in the treatment of early syphilis has also been advocated.¹⁰³ Small groups of patients were treated with varying amounts of penicillin and concurrent hyperpyrexia. The results showed that smaller amounts of penicillin were necessary to cure early syphilis when administered in conjunction with fever therapy. Too little has been done with this to warrant definitive statements regarding dosage. Appraisal of these reports on the penicillin treatment of early syphilis will clearly indicate that dosage schedules, time-dose relations and combined-therapy methods require a great deal of further study before optimal programs are worked out.

Penicillin during Pregnancy

It has been demonstrated by a number of observers that penicillin passes through the placenta in sufficient amounts to provide an adequate bacteriostatic level in the fetal circulation.¹⁰⁴⁻¹⁰⁶ The obvious inference is that penicillin should eradicate syphilitic infections in both the mother and fetus. Since transmission to the fetus has been shown as early as the tenth week of gestation,¹⁰⁷ satisfactory treatment of prenatal syphilis early in pregnancy should be readily accomplished. There are clinical reports indicating that this is a safe and effective procedure. The penicillin treatment of groups of pregnant syphilitic women in Baltimore and Philadelphia clinics exhibited highly successful results in the prevention of congenital syphilis.^{108, 109} It was found that reversal of the mother's blood serologic tests to negativity was not necessary to produce a normal infant. Many infants who were born with positive serologic reactions became negative within a month's time. All the mothers had early syphilis, some were treated as late as the thirty-second week in pregnancy. A reduced initial penicillin dosage for the first forty-eight hours is advocated to avoid possible reactions. The Baltimore group believes that any suggestion that penicillin has abortifacient effects is unwarranted. It is advisable to follow the pregnant woman clinically and with repeated titrated serologic tests at least once a month until delivery and at appropriate intervals thereafter. Retreatment with penicillin should be given to the mother during pregnancy if there is evidence of clinical or serologic relapse or if the original maternal serologic titer does not significantly decline within three months after treatment. It is believed that, pending further information, a pregnant syphilitic woman whose infection has apparently been previously treated successfully with penicillin should be retreated with penicillin in each succeeding pregnancy.

Congenital Syphilis

Although the earliest reports regarding the penicillin treatment of congenital syphilis were not so optimistic as those in other forms of the disease, later publications are somewhat more encouraging.

The most satisfactory results have been obtained in cases of early congenital syphilis with manifest symptoms^{110, 111}. In patients with asymptomatic early congenital syphilis there is no clinical guide, but a gradual decrease in the titer of the blood may be observed in most cases. In late congenital syphilis, especially among patients with interstitial keratitis and neurosyphilis, clinical and laboratory findings indicate a much poorer response¹¹⁰. The penicillin treatment of syphilis in infants and children, either the congenital or the acquired disease, leaves much to be desired¹¹². Dosage schedules so far recommended vary from 20,000 units per kilogram of body weight (divided into sixty doses)¹¹³ to as high as three times that amount^{110, 114}. Periods of administration of from seven and a half to twenty days have been advocated.

Late Syphilis

The predominant attention to the use of penicillin in syphilis has been directed toward early infections. A few reports regarding management of the later stages of the disease are becoming available. A small group of patients with benign late gummatous syphilis were treated and followed for an average period of about fourteen months¹¹⁵. Cutaneous, mucocutaneous and mucous-membrane gummas, osseous lesions and hepatic gummas were included. The minimal dosage was 2,000,000 units, and the maximum was 4,000,000 units in some cases. There was a relatively rapid symptomatic response in all patients, although the objective findings in the hepatic cases were slower to improve. There was also a case of incidental gummatous keratitis that responded satisfactorily.

Syphilitic Nephrosis

One of the less frequent but more spectacular symptoms of syphilis is acute syphilitic nephrosis. The patients develop marked and widespread edema, with gross proteinuria and critically reduced plasma proteins. To establish the diagnosis, syphilis must be proved, with the absence of other urinary findings and lack of evidence of any of the usual causes of nephrosis. Two cases of rather dramatic response of acute syphilitic nephrosis to treatment with penicillin were recently reported^{116, 117}.

Ocular Syphilis

Syphilis can affect the eye in many ways, and the treatment in these cases requires considerable care. The eye is an organ in which the occurrence of a Herxheimer reaction may cause extremely unfortunate destruction. In a group of 17 patients with iritis associated with the lesions of early syphilis who were treated with penicillin alone, the incidence of Herxheimer reactions was kept down by properly reduced initial dosage¹¹⁸. Treatment was started with 5000 to 20,000 units, the dosage being gradually

increased to 50,000 to 60,000 units, with satisfactory beneficial effects.

Cardiovascular Syphilis

There has been considerable hesitancy on the part of cardiologists regarding the use of penicillin in cardiovascular syphilis¹¹⁹. This uncertainty is not shared by most syphilologists, although more care is exerted in the plan of treatment employed. It is a well known fact that Herxheimer reactions can be prevented by steadily increasing doses of any drug used in the treatment of syphilis. Even when initial therapy is low in dosage, a repetition of the same small amount may be followed by a Herxheimer reaction. It is quite likely that the pursuance of this policy would be accompanied by extremely few cases of reaction to penicillin in cardiovascular syphilis.

Neurosyphilis

There were for a time conflicting reports regarding the penetration of penicillin into the spinal fluid, regardless of means of administration other than intrathecal. Further reports indicate that systemic administration of penicillin in doses generally used will not consistently produce measurable levels of penicillin in the spinal fluid¹²⁰. There is apparently a somewhat greater tendency for the drug to reach the subarachnoid space in the presence of meningitis. Therapeutic spinal-fluid levels of penicillin are not attained unless blood serum levels much higher than the usual minimal effective quotient are maintained for periods of twelve hours or more. Massive doses of penicillin by continuous intravenous drip were followed by the appearance of penicillin in significant amounts in the spinal fluid of a large percentage of patients¹²¹. The use of fever in conjunction with intramuscular penicillin does not appear to affect the concentration of penicillin reaching the spinal fluid¹²². The penetration of penicillin through the meninges seems to be irregular and unpredictable in meningeal infections of all types¹²³.

Nevertheless, there are ample reports substantiating the value of penicillin in the treatment of various forms of neurosyphilis. Again, some of the best results have been obtained when the drug is used in conjunction with other forms of therapy. Large and small groups of cases, including all types of neurosyphilis, have shown encouraging results, except in the end stages of general paresis^{92, 124-133}. Smaller amounts of penicillin and shorter courses of fever therapy have been found necessary when given concurrently or in succession than when either was used alone. The use of this combination in primary optic atrophy is quite encouraging. It is the opinion of most observers that all forms of parenchymatous neurosyphilis require fever therapy as well as penicillin. Some state that improvement with penicillin appears sooner than with other methods, it is fre-

quently manifested within a few months, rather than as long as a year or more after malaria therapy. The most striking effects of penicillin are exerted on the spinal-fluid formula, where some improvement may be noted by the time therapy is terminated. There is no correlation between spinal-fluid response and the effect on blood serologic findings. The symptomatic phases of *tabes dorsalis* respond to penicillin therapy to an encouraging extent, with the exception of Charcot joints. Whereas penicillin alone is apparently no better than malaria alone and probably is not so effective, the two together appear to enhance each other's effect. Dosage schedules of penicillin for neurosyphilis have varied widely, from 4,000,000 to 10,000,000 units being advocated. Some observers consider repeated courses of penicillin at intervals of a few months more beneficial, but in general the higher dosage programs with prolongation of the time of administration of a single course are preferred. There is fairly general agreement that penicillin alone is not capable of controlling the graver forms of parenchymatous neurosyphilis.

The intrathecal administration of penicillin continues to receive some attention. When introduced in this manner the drug is known to remain in the spinal fluid for periods of twenty-four to seventy-two hours. The injections are given by the Swift-Ellis technic. Treatments may be given daily or as much as a week apart, the suggested doses are at great variance.¹³⁴⁻¹³⁶ The number of treatments that can or should be given has not yet been determined. Intrathecal penicillin may be used in cases in which malaria therapy is contraindicated, and the results are encouraging. Combined intraspinal and intramuscular penicillin has also been advocated. This method is certainly not yet adaptable for general use, since some serious reactions have occurred.

Reactions to Penicillin

In general, it may still be said that reactions to penicillin therapy have been fewer and milder than those with any form of treatment for syphilis heretofore devised. Nevertheless, as with practically every new drug of any sort, an increasing number and variety of side actions have been observed.

The Herxheimer reaction is perhaps the most frequent and is of little importance in early syphilis, but may be dangerous in several forms of visceral syphilis. This may be avoided by starting with small doses (as little as 1000 units) and gradually increasing to the optimum dose.

Urticaria has been observed rather frequently and is, as a rule, merely a troublesome affair. Angioneurotic edema is less frequent but may even prove fatal.¹³⁷ Fungous infections are not infrequently aggravated,^{92, 138, 139} and the so-called "id eruptions" may appear, either epidermophytids or bacterids.¹⁴⁰ It is believed by some investigators that a previous acute fungous infection may cause increased re-

activity to penicillin.¹⁴¹⁻¹⁴³ The tissue primarily affected in most penicillin reactions is reported to be the blood vessels rather than the epidermis. Purpuric eruptions and severe arthralgia have occurred.¹³⁹ A syndrome similar to serum sickness has been observed on a number of occasions.¹⁴¹⁻¹⁴⁶ Eruptions typical of toxic erythema multiforme have been described, as have those characteristic of erythema nodosum.¹⁴⁵ Aggravation of a considerable variety of pre-existing skin diseases has been reported.¹³⁸ Contact dermatitis is not infrequently observed,¹⁴⁶⁻¹⁵⁷ including involvement of the eyelids. This is of the greatest significance among medical personnel and laboratory workers handling penicillin solutions over long periods.

I have observed a case of an extremely severe reaction to penicillin that nearly caused death. So far as could be ascertained from the preceding physicians, the patient had received no other drug known to be capable of causing dermatitis. After three days of penicillin therapy for an upper respiratory infection, the patient developed a toxic eruption similar to erythema multiforme. Within twenty-four hours it became generalized, and mucous-membrane lesions interfered with the taking of nourishment. On the third day there were dysphagia and nausea, indicating probable lesions of the gastrointestinal tract. Generalized edema and exfoliative dermatitis quickly followed. Six weeks of hospitalization were required for recovery.

Decreased Potency

Unfortunate publicity by the lay press gave rise to doubts in the mind of the general public and many physicians regarding the efficacy of penicillin during the past year. There were some grossly inaccurate and irresponsible statements in the newspapers before any official scientific report could be prepared and released. It became known to those most closely following penicillin research toward the middle of 1944 that the treatment of syphilis with this drug was somewhat less satisfactory. Many wheels were immediately set turning to decipher the cause, and eventually it was found that the increased purity of commercial penicillin was at fault. There are several penicillins, and penicillin K has been shown to be of little or no value in the treatment of syphilis, as well as certain other infections, because it is too rapidly destroyed in the body.¹⁵³ As commercially supplied by some manufacturers in a purer form, far larger amounts of penicillin K were included, the amount was not large enough to cause a serious reduction in the value of penicillin in the treatment of syphilis and need not have caused alarm. Progressively less penicillin K is now found in commercial preparations, and the situation has meanwhile been controlled by the mere increase of penicillin dosage in the treatment of syphilis. An official statement on the use of penicillin in syphilis was finally released

after the appearance of newspaper publicity.¹⁵⁹ Subsequently, a full report was published giving suggestions regarding the use of the drug in the treatment of syphilis.^{160, 161}

Although the best method for the employment of penicillin in the treatment of syphilis cannot be arbitrarily stated, certain minimum suggestions for treatment were given. For seronegative primary syphilis not less than 3,600,000 units was advised, and for seropositive primary and early secondary syphilis, not less than 5,400,000 units seemed imperative. In cases of relapse, including possible reinfection, after previous treatment, the course of 5,400,000 units should be repeated, followed by 360 mg of Mapharsen or an analogous drug given twice to three times weekly in six individual intravenous injections of 60 mg each, in addition to 1200 mg of bismuth subsalicylate given twice weekly in six individual intramuscular injections of 0.2 gm each. For a second relapse of early syphilis after previous penicillin treatment the patient should be transferred from penicillin entirely and placed on intensive metal therapy. Further recommendations were given for the management of various other phases of syphilis and its complications. The administration of penicillin in oil and wax for the treatment of syphilis has not been worked out sufficiently to be considered satisfactory. Under no circumstances should penicillin in its present available form be administered orally for the treatment of syphilis. The changing character of commercial penicillin and the consequent alteration in plans of administration should serve to emphasize that penicillin therapy for syphilis is still incompletely evaluated. It will take some years of further work and careful follow-up study before the actual status of this drug in the management of syphilis can be finally determined.

SUMMARY

The release of several million young men from military duty places a greater burden than ever on public-health facilities in the prevention of venereal disease. The responsibility is squarely back on the shoulders of every state and local board of health, although the United States Public Health Service is still carrying on large-scale control measures. Education of the public continues to be of inestimable value in this respect.

The state of Alabama is continuing its legally required mass blood-testing program with extremely satisfactory results.

Studies of mortality on a nationwide basis indicate that the death rate from syphilis is slowly but steadily decreasing. Figures indicate that untreated syphilis may reduce the span of life by as much as 20 per cent. Properly treated syphilis, however, will shorten the life expectancy only about half as much.

Serologic problems in the diagnosis of syphilis and false-positive blood tests continue to be a

stumbling block. The question of reinfection of the human being with *Treponema pallidum* may have been overemphasized in the face of rapid cures by recent methods of intensive therapy and by the use of penicillin. Advocates of any form of treatment may be too reluctant to admit the likelihood of relapse.

A most instructive ten-year study of late syphilis has finally appeared, showing conclusively that adequate antisyphilitic treatment reduces the hazard of late serious complications to a minimum even though the blood serologic reactions may not reverse to negative.

A survey of a large group of patients undergoing lumbar punctures suggests that the emotional reaction of the patient may be of great importance in the incidence of post-puncture headaches.

The treatment of syphilis seems to swing ever farther away from the massive dose five-day schedules. Multiple injection programs over short periods have proved much safer. One of the most important advances in combating treatment reactions is the use of BAL (2,3-dimercaptopropanol). This drug has been found to be remarkably effective in the systemic treatment of several forms of severe arsenic poisoning. Urinary excretion of arsenic is strikingly increased, and side actions from this drug are comparatively few. Such complications as hemorrhagic encephalitis, exfoliative dermatitis, agranulocytosis and post-arsphenamine jaundice have shown most gratifying response.

The greatest emphasis in the treatment of syphilis will continue to lie in the use of penicillin. Experimental studies with the various penicillins, regarding methods of administration, effects on specific organisms, the possible development of resistance and so forth continue. As yet, the use of the highly soluble forms of penicillin, with frequent injections over periods of some days, is the only acceptable method of administration. Less frequent administration in oil and wax may prove to be suitable. The combination of penicillin with arsenotherapy and the concurrent use of penicillin with hyperpyrexia seem to hold the greatest promise. One pitfall is the possibility of masking early syphilis with the use of small amounts of penicillin for the treatment of gonorrhea, many cases have been reported. The greatest volume of penicillin therapy has been given in early syphilis, but as yet an entirely satisfactory schedule has not been worked out. Its use in other forms of the disease lags somewhat but is also encouraging. Reactions to penicillin have increased in number and variety but have rarely been grave.

Perhaps the best example of the fact that penicillin therapy for syphilis should still be considered largely experimental is the altered potency of this drug. A number of commercial preparations have been found to contain large proportions of a type of penicillin that is comparatively ineffective against syphilis. This has necessitated marked increases in

the amount of the drug necessary to provide satisfactory response. It can hardly be said that a great deal more is known about the effectiveness or long-term value of penicillin at present than a year ago. It must again be stated that much more work and many more years will elapse before satisfactory programs are established.

REFERENCES

46. Leifer W. Danger of continued arsenotherapy in cases of erythema of ninth day. *Am J M Sc* 210:458-463 1945
57. McManus J F. Agranulocytosis following Mapharsen therapy: report of two cases treated with penicillin. *Am Eng J Med* 234:17-19 1946
58. Shapiro A. L. Colloidal shock following injection of oxophenarsene hydrochloride (mapharsen): report of case. *Arch Dermat & Syph* 52:595 1945
59. Marshall J. Nature of icterus due to administration of arsenophenarsene compounds to syphilitic. *Progress* 73:310 1945
60. Hinds E., and Katz, F. Studies on liver function. II. Value of laboratory tests in prevention of arsenical toxicity: with report of two unusual cases of encephalopathy. *Am J Syph., Gonorr & Ven Dis* 30:70-81 1946
61. Eagle H. Systemic treatment of arsenic poisoning with BAL (2-mercaptopyracol). *J Ven Dis Inform* 27:114-121 1946
62. Cutting W. C., Ludueña F. P., Fiese, M. Elliott, H. W., and Field J. H. Distribution and fate of penicillin in body. *J Pharmacol & Exper Therap* 85:36-41 1945
63. Lee S. W. and Foler E. J. Effect of temperature on action of penicillin in vitro. *Proc Soc Exper Biol & Med* 60:133-136 1945
64. Ory E. M., Meade M., and Finland M. Penicillin N: comparison with penicillin G with respect to sensitivity of pathogenic organisms and serum levels. *J A M A* 129:257-261 1945
65. Olansky S., and Putnam L. E. Effect of sodium salts of crystalline penicillin G: crystalline penicillin N, and commercial penicillins on darkfield positive lesions of syphilis. *J Ven Dis Inform* 27:178-180 1946
66. Frazier C. N., and Frieden, E. H. Action of penicillin especially on *Treponema pallidum*. *J A M A* 130:677-683 1946
67. Tang T. and Frazier C. N. Penicillin sensitivity and morphology of Reiter strain of *Treponema pallidum* after cultivation in media containing penicillin. *Am J Syph., Gonorr & Ven Dis* 30:205-210, 1946
68. Tainter M. L. Summary of problems of sulfa and penicillin fastness. *New York State J Med* 45:2509-2514 1945
69. Tyson W. G. Early syphilis resistant to treatment with penicillin: report of case. *J Intern Dermat* 6:279-281 1945
70. Finland M., Meade M., and Ory E. M. Oral penicillin. *J A M A* 129:315-320 1945
71. Ross S., Burke F. G. and McLendon P. A. Penicillin by mouth: report of clinical trial. *J A M A* 129:327-332 1945
72. Burns P. A. Treatment of infections with penicillin given orally. *Internist* 12:182 1946
73. Departments of Pharmacology and Medicine, Cornell University Med. College and The New York Hospital. Conference on Therapy. Oral penicillin. *New York State J Med* 46:527-534 1946
74. Gröry P., Evans K. W., Rose E. K., Perlino J. G. and Elias W. F. Oral penicillin. *Pennsylvania M J* 49:409-416 1946
75. Romaszyk M. J., and Rittman, G. E. Penicillin blood levels for twenty-four hours following single intramuscular injection of calcium penicillin in beeswax and peanut oil. *New Eng J Med* 233:577-582 1945
76. Kirby W. M. M., Martin S. P., Leifer W., and Kinsman J. M. Maintenance of therapeutic blood concentrations of penicillin for twenty-four hours following single injections of penicillin-beeswax peanut oil mixtures. *J Lab & Clin Med* 31:313-316 1946
77. Nichols D. R., and Haunz, E. A. Prolonged action of penicillin in mixtures of beeswax and peanut oil. *Proc Staff Meet. Mayo Clin* 20:403-407 1945
78. Kirby W. M. M., Leifer W., Martin S. P., and Rammelkamp C. H. Intramuscular and subcutaneous administration of penicillin in beeswax peanut oil. *J A M A* 129:940-944 1945
79. Bohls S. W. and Cook, E. B. M. Use of aluminum penicillin mixtures in maintenance of blood levels of penicillin. I. Intramuscular injections of aluminum-penicillin. *Texas State J Med* 41:249-252 1945
80. *Idem*. Use of aluminum penicillin mixtures in maintenance of blood levels of penicillin. II. Combination of delayed absorption by use of aluminum penicillin and renal blockage with benzoic acid. *Texas State J Med* 41:342-344 1945
81. Bohls S. W., Cook, E. B. M., and Potter R. T. Oral and parenteral use of aluminum penicillin mixtures in treatment of gonorrhea. *J Ven Dis Inform* 27:69-74 1946
82. Magnuson H. J. and Eagle H. Retardation and suppression of experimental early syphilis by small doses of penicillin comparable to those used in treatment of gonorrhea. *Am J Syph., Gonorr & Ven Dis* 29:587-596 1945
83. Walker, A. E. and Barton R. L. Treatment of gonorrhea with penicillin during incubation period or early phase of syphilis—review. *J Ven Dis Inform* 26:241-244 1945
84. Scarcello N. S. Warnings in use of penicillin. *U S A M Bull* 45:77-79, 1945
85. Derzavits J. L. and Bond F. T. Suppression of early syphilis by subtherapeutic dosage of penicillin: report of case. *U S A M Bull* 46:259-261, 1946
86. Miller T. H. Effects of small doses of penicillin administered to patients with undiagnosed early syphilis. *J Michigan M Soc* 45:353-355 1946
87. Leifer W., and Martin S. P. Effect of penicillin on course of early syphilis. *J A M A* 130:202-205 1946
88. Fromer, S., Cutler J. C., and Levitan, S. Masking of early syphilis by penicillin therapy in gonorrhea. *J Ven Dis Inform* 27:174-177 1946
89. Pillsbury D. M. Penicillin therapy of early syphilis: follow-up examination of 792 patients six or more months after treatment. *Brit J Ven Dis* 21:139-150 1945
90. *Idem*. Penicillin therapy of early syphilis in 14 000 patients: follow-up examination of 792 patients six or more months after treatment. *Am J Syph., Gonorr & Ven Dis* 30:134-143 1946
91. Schoch A. G. and Alexander L. J. Treatment of early syphilis with penicillin. *J A M A* 130:696-698 1946
92. Barksdale E. E. Penicillin in treatment of syphilis: results and complications. *South M J* 39:229-235, 1946
93. Penicillin progress report based on 1455 cases treated at National Naval Medical Center, Bethesda Maryland. *U S A M Bull* 44:451-479 1945
94. Callaway, J. L. Present concept of treatment of syphilis with penicillin. *South Med & Surg* 108:76 1946
95. Leifer W. Treatment of early syphilis with penicillin. *J A M A* 129:1247-1251 1945
96. Marshall J. Penicillin in treatment of syphilis. *Nature (London)* 156:769-772, 1945
97. Preventive Medicine. Penicillin treatment of syphilis. *Bull U S Army Med Dept* 4:324 1945
98. Becker S. W. Penicillin in treatment of syphilis. *J Michigan M Soc* 44:1195-1198 1945
99. Baker C. G. Penicillin in treatment of syphilis. *Kentucky M J* 43:327-332 1945
100. Bell W. J. Penicillin treatment of early syphilis. *Rhode Island M J* 28:884 1945
101. Olansky S. and Chinn B. D. Present status of penicillin therapy for syphilis. *M Arr. District of Columbia* 15:204-208 1946
102. Eagle H., Magnuson H. J. and Fleischman R. Synergistic action of penicillin and mapharsen (oxophenarsene hydrochloride) in treatment of experimental syphilis. *J Ven Dis Inform* 27:3-9 1946
103. Craig R. M., Schwemlein G. N. and Kendall H. W. Penicillin combined with fever therapy: preliminary report of twenty cases of early syphilis. *J Lab & Clin Med* 30:1016-1020 1945
104. Herrell W. E., Nichols D. R., and Heilmann D. H. Penicillin: its usefulness, limitations, diffusion and detection with an analysis of 150 cases in which it was employed. *J A M A* 125:1003-1011 1944
105. Greene H. J. and Hobby G. L. Transmission of penicillin through human placenta. *Proc Soc Exper Biol & Med* 57:282 1944
106. Hutter A. M. and Parks J. Transmission of penicillin through placenta: preliminary report. *Ar J Obst & Gynec* 49:663-665 1945
107. Woltz, J. H. E. and Wiley M. M. Transmission of penicillin to previsible fetus: its significance in prenatal syphilis. *J A M A* 131:969 1946
108. Ingraham N. R. Jr., Stokes J. H., Beerman H., Lentz J. W., and Wammock A. S. Penicillin treatment of syphilitic pregnant woman. *J A M A* 130:683-688 1946
109. Goodwin M. S. and Moore J. E. Penicillin in prevention of prenatal syphilis. *J A M A* 130:688-694 1946
110. Wilkinson E. E., Saunders W. H. and Hansen, A. E. Penicillin in treatment of congenital syphilis. *Texas State J Med* 41:401-404 1945
111. Heyman A. and Lampolsky J. Treatment of infantile congenital syphilis with penicillin. *Am J Dis Child* 71:505-512 1946
112. Neilson A. W., Chard F. H., Klingberg W. G., Hanchett L. J., Gabby W. H., Rodriguez, J., and Watkins, C. Treatment of congenital and of acquired syphilis in infants and in children by penicillin. *Arch Dermat & Syph* 53:625-632 1946
113. Ingraham N. R., Jr., Stokes J. H., Beerman, H., Lentz J. W., Gröry P. and Rose E. K. Penicillin treatment of syphilitic infant. *J A M A* 130:694-696 1946
114. Watson E. R. Early congenital syphilis: diagnostic criteria and penicillin therapy. *J M A Georgia* 34:200 1945
115. Dexter D. D. and Tucker, H. A. Penicillin treatment of benign late gummatous syphilis: report of twenty-one cases. *Am J Syph., Gonorr & Ven Dis* 30:211-226 1946
116. Holman, D. V., and Makovsky, I. H. Acute syphilitic nephrosis treated with penicillin. *New York State J Med* 46:520-522 1946
117. Barr J. H. Jr., Cole H. N., Driver, J. R., Leas R. D., Miller M., and Strauss L. G. Acute syphilitic nephrosis successfully treated with penicillin. *J A M A* 131:741-745 1946
118. Klauder J. V. and Dublin G. J. Syphilitic uveitis: diagnosis, Herxheimer reaction and results of various treatments including penicillin therapy. *Arch Ophth* 35:384-399 1946
119. Dolkart R. E., and Schwemlein G. N. Treatment of cardiovascular syphilis with penicillin. *J A M A* 129:515 1945
120. Dumoff-Stanley E., Dowling H. F., and Sweet L. K. Absorption into and distribution of penicillin in the cerebrospinal fluid. *J Clin Investigation* 25:87 1946

- 121 Schwemlein G N, Barton, R L, Bauer, T J, Loene L, Bundesen H N, and Craig, R M. Penicillin in spinal fluid after intravenous administration. *J A M A* 130 340 1946
- 122 Kaplan, L I, Read H S, Becker, F T, and Seymour, C F. Concentration of penicillin in spinal fluid following intramuscular administration in neurosyphilis: negative report. *J Lab & Clin Med* 31 317-322, 1946
- 123 Kinsman, J M, and DeAlonzo, C A. Penetration of penicillin through normal and inflamed meninges. *New Eng J Med* 234 459-464, 1946
- 124 Rose, A S, Trevett, L D, Hindle, J A, Prout, C, and Solomon H C. Penicillin treatment of neurosyphilis: preliminary report of 70 cases followed from four to twelve months. *Am J Syph, Gonorr & Ven Dis* 29 487-493 1945
- 125 Rose A S. Penicillin treatment of neurosyphilis. *Connecticut M J* 9 522-525, 1945
- 126 Callaway, J L, Noojin, R O, Flower, A H, Jr, Kuhn, B H, and Riley, K A. Use of penicillin in treatment of syphilis of central nervous system: report of 100 patients. *Am J Syph, Gonorr & Ven Dis* 30 110-124 1946
- 127 O'Leary, P A, Brunsting, L A, and Ockuly, O. Penicillin in treatment of neurosyphilis. *J A M A* 130 698 700 1946
- 128 Stokes, J H, Steiger H P, Gammon G D, Steele W H, Beerman, H, Ingraham, N R, Jr, György, P, Rose, E, and Lentz, J W. Penicillin alone in neurosyphilis. *J A M A* 131 1-7, 1946
- 129 Callaway J L, Noojin R O, Kuhn, B H, Riley, K A, and Sergerson, J A. Syphilitic arachnoiditis treated with penicillin. *Am J Syph, Gonorr & Ven Dis* 30 231-234 1946
- 130 Nelson R A, and Moore, J E. Acute syphilitic meningitis treated with penicillin: progress report. *Am J Syph, Gonorr & Ven Dis* 30 227-230, 1946
- 131 Reynolds F W, Mohr, C F, and Moore J E. Penicillin in treatment of neurosyphilis. II Dementia paralytica. *J A M A* 131 1255 1260 1946
- 132 Rosanoff, W R, and Norman, J K. Report of two cases of paresis treated with penicillin. *South M J* 38 819 822 1945
- 133 Stern, J E, and Campbell, H M. Early effects of penicillin treatment of dementia paralytica: clinical and psychologic study. *Arch Neurol & Psychiat* 55 266-273 1946
- 134 Thrasher, J R. Intrathecal penicillin in cerebral spinal syphilis. *J Indiana M A* 38 216-220 1945
- 135 Rubin S H, and Leitch C G. Intrathecal penicillin in treatment of neurosyphilis: preliminary report. *J Missouri M A* 43 169 171 1946
- 136 Weickhardt G D. Intrathecal administration of penicillin in general paresis. *Am J Syph, Gonorr & Ven Dis* 30 235 241 1946
- 137 Strickland D A. Penicillin sensitivity: angioneurotic reaction. *U S Nav M Bull* 45 768 1945
- 138 Kolodny, M H, and Denhoff E. Reactions in penicillin therapy. *J A M A* 130 1058-1061 1946
- 139 Price I C. Severe allergic reaction to intramuscular penicillin. *Canad M A J* 53 485 1945
- 140 Heinlein, J A, Carpenter, C C, and Duff, B J, Jr. Aggravation of bacterids by penicillin: with theory as to causation. *U S Nav M Bull* 46 571-575 1946
- 141 Cormia, F E, Jacobsen, L Y, and Smith, E. L. Reactions to penicillin. *Bull U S Army M Dept* 4 694-702, 1945
- 142 Sullens W E, Jr. Simulating serum-sickness reaction to penicillin. *U S Nav M Bull* 45 752 754, 1945
- 143 Strazza, J A, Jr. Delayed sensitization to penicillin similar to serum sickness. *J A M A* 130 1071, 1946
- 144 Haswell R E, and Wilkinson, J F. Allergic reaction to parenteral penicillin. *Lancet* 1 308, 1946
- 145 Lamb, J H. Allergic reactions during administration of penicillin. *Arch Dermat & Syph* 52 93 95, 1945
- 146 Gottschalk H R, and Weiss R S. Epidermal sensitivity to penicillin. *Arch Dermat & Syph* 53 365-371, 1946
- 147 Goodman H. Dermatitis due to preparation and administration of penicillin solution. *Arch Dermat & Syph* 54 206-208, 1946
- 148 McGuire, J A. Localized sensitivity to crude penicillin: report of case. *Arch Dermat & Syph* 53 31 33, 1946
- 149 Markson L S. Dermatitis venenata following use of penicillin ointment. *Arch Dermat & Syph* 52 384 1945
- 150 Bedford P D. Case of penicillin dermatitis. *Brit M J* 1 51 1946
- 151 Benkwith, K. B. Allergy to penicillin: calcium topically in blepharoconjunctivitis. *U S Nav M Bull* 46 279 1946
- 152 Goldman, L, Friend F, and Mason L M. Dermatitis from penicillin. *J A M A* 131 883-890 1946
- 153 Vorisek E A, and Evans A L. Penicillin administered locally in gonorrheal ophthalmia: sensitization reaction. *Am J Ophth* 28 520 523 1945
- 154 Bechet P E. Induced sensitivity from topical use of sulfonamides and penicillin. *Pennsylvania M J* 49 417-420, 1946
- 155 Schultz, A. Ocular dermatitis from local penicillin: report of two cases. *Arch Ophth* 35 145 149, 1946
- 156 Satuleky, E. M. Dermatitis venenata of eyes and eyelids from local use of penicillin. *J M Soc New Jersey* 43 95 1946
- 157 Vickers H R. Contact dermatitis caused by penicillin. *Lancet* 1 307 1946
- 158 Eagle, H, and Musselman A. Low therapeutic activity of penicillin K relative to that of penicillins F, G and X, and its pharmacological basis. *Science* 103 618-620, 1946
- 159 Current Comment. Official statement on penicillin in syphilis. *J A M A* 131 34 1946
- 160 Committee on Medical Research and United States Public Health Service. Treatment of early syphilis with penicillin. *J A M A* 131 265-271, 1946
- 161 Committee on Medical Research, United States Public Health Service and Food and Drug Administration. Changing character of commercial penicillin with suggestions as to use of penicillin in syphilis. *J A M A* 131 271 275 1946.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 33081

PRESENTATION OF CASE

A fourteen-month-old boy was brought to the hospital in a semistuporous condition.

The patient had been born in the eighth month of pregnancy after premature spontaneous rupture of the fetal membranes. The mother was well. The father, an Army veteran, had had malaria and suffered from hay fever. No difficulties attended the delivery, and the infant was subsequently well until the onset of the present illness. He talked at one year and before admission was walking with help. Three months before admission, a nystagmus was noted. One month later the appetite began to fail, and in the two months before admission there was a weight loss of 2 pounds. Immunizations against diphtheria, pertussis and tetanus were carried out during the same period. In the month before admission a habit of pounding the fists on the head was noted, but in general the child was not thought to be sick until a week before admission, when a moderate upper respiratory infection with laryngitis developed. This cleared without special treatment, and the patient was well until the day of admission. At breakfast he seemed feverish and restless. The mother administered an enema, the return being gray green. Afterward the patient screamed continuously for two hours, doubled up, closed his eyes and put back his head. The temperature was found to be elevated. He vomited four times and could not retain fluid.

Physical examination showed the skin and scleras to be faintly yellow. The head measured 47 cm., and the chest 45 cm. in circumference. There was a slight left lateral nystagmus, as well as tonic deviation of the eyes to the left. The pupils were equal and reacted to light. The fundi were normal, as were the nose and ears. Slight weakness of the right lower facial muscles was observed. The pharynx was slightly reddened. The neck resisted flexion. The heart, lungs and abdomen were normal. The patient moved all extremities freely. The limb reflexes were normal, but the abdominal reflexes were absent.

The temperature was 105°F, the pulse 190 and the respirations 34.

Examination of the blood disclosed a red-cell count of 4,200,000 and a white-cell count of 17,000, with 62 per cent neutrophils.

No urine was obtained until the second day after glucose had been given intravenously. Then only a small amount was obtained, which showed an orange sugar reaction and a +++ test for acetone. The initial lumbar puncture yielded several cubic centimeters of bloody fluid that was slightly, but definitely, xanthochromic after centrifugation. The pressure was increased, but the patient was sitting and crying. Microscopically, the fluid contained innumerable red cells, as well as 60 lymphocytes per cubic millimeter and no polymorphonuclear cells. No organisms were found. The Pandy test was strongly positive. The protein was 440 mg., and the sugar 76 mg. per 100 cc. and the chloride 126 milliequiv. per liter.

X-ray examination of the skull was negative. Abundant colonies of alpha-hemolytic streptococci were cultured from the throat. There was no growth from the spinal fluid on chocolate agar. The blood-agar plate was contaminated.

The immediate treatment consisted of intravenous fluids and intramuscular penicillin. The temperature and pulse had fallen to normal by the second day, but soon began to rise again. Only 3 drops of pink fluid under little pressure were obtained on two additional lumbar taps. The fluid contained 80,000 red cells, of which 20 per cent were crenated, and 60 lymphocytes per cubic millimeter. On the afternoon of the same day the neurologic findings were somewhat altered. The right facial weakness was absent, and the eyes were held straight, deviating only occasionally to the right and left. The plantar reflexes were extensor. The patient was restless and irritable. Three hours later he was deeply comatose, with gasping respirations at a rate of 16 per minute. The reflexes were depressed. There was an erythematous macular rash on the cheeks and trunk that did not fade on pressure. On the same evening, he stopped breathing while being prepared for operation. The air passages were suctioned, and manual oxygen insufflation through an intratracheal tube was carried out. An operation was then performed.

DIFFERENTIAL DIAGNOSIS

DR. JOST J. MICHELSEN: I think it will be agreed that there is little information in this record to help us in arriving at a satisfactory conclusion. Of course, a neurologic diagnosis in this age group is always difficult, since the history and the results of examination are, as a rule, incomplete. In the case under discussion information is even more scanty than in the average.

It is almost certain that the patient had some sort of intracranial disease. We might even go a step farther and say that there was probably increased

intracranial pressure Apparently, there was terminal respiratory failure, which is a common occurrence in cases with increased intracranial pressure Before I continue with the discussion, however, I should like to ask two questions, How should one interpret the erythematous macular rash on the cheeks and trunk during the terminal phase of the disease, and what is the significance of the sugar and acetone found in the urine?

DR ALLAN M BUTLER I do not know the significance of the rash I did not see it So far as the sugar in the urine is concerned, according to the abstract the first specimen was obtained after intravenous glucose was started

A PHYSICIAN It was obtained after the intravenous drip had been administered for twenty-four hours

DR MICHELSEN Is it usual for acetone to be present with such intravenous glucose?

DR BUTLER If the urine was obtained after twenty-four hours of intravenous glucose and the patient did not have diabetes, the acetonuria was unusual

DR MICHELSEN Let us scrutinize the data that might help to determine the type of lesion that this patient had We are told that there was rigidity of the neck As is well known, rigidity of the neck is most frequent with intracranial infections, particularly with those of the subarachnoid and subdural spaces, it also occurs as a manifestation of meningeal irritation following hemorrhage into the subarachnoid and subdural spaces Less often, it is found in association with tumors that occupy the posterior fossa or as a result of herniation of the cerebellar tonsils into the foramen magnum There is no evidence that the patient had intracranial sepsis, notwithstanding the fact that a few days prior to the onset of the more recent manifestations there was an upper respiratory infection Offhand, there is also no evidence that the child had a brain tumor This leaves, as the only alternative, an intracranial hemorrhage The cerebrospinal-fluid findings suggest that this hemorrhage occurred into either the subarachnoid space or the ventricular system, or perhaps both The question then arises, How much significance should be attributed to the cerebrospinal-fluid findings of 80,000 red cells and 60 lymphocytes per cubic millimeter? There seems to be something wrong in this observation Considering the high white-cell count in the blood—17,000, with 62 per cent neutrophils—and the number of red cells in the spinal fluid, one would expect about 200 polymorphonuclears in the spinal fluid Apparently, only red cells and lymphocytes were found The differential count could not have been correct It is said that the fluid after the initial lumbar puncture, which contained a large number of red cells, was definitely xanthochromic after centrifugation I should expect any grossly bloody cerebrospinal fluid to show discoloration of the supernatant fluid

after centrifugation, since, of course, it is mixed with serum I should also assume that this lumbar puncture was difficult, since a routine lumbar puncture is not performed in the sitting position As a rule, if possible, we use three test tubes to determine the source of blood in the cerebrospinal fluid If the cerebrospinal fluid is equally bloody in all three, we are compelled to assume that the bleeding has occurred prior to the lumbar puncture, most probably in the intracranial cavity If, however, the appearance of the fluid changes and the second and third fluid portion look clearer and contain less blood than the first one, it is likely that the blood originated from the site of the puncture Is there any information regarding this point in the hospital record?

A PHYSICIAN No, only one tube was used, since the fluid came out as if under pressure

DR MICHELSEN There was actually increased pressure, then

Let us assume that an intracranial hemorrhage had occurred and discuss some of the causes of such an event A hemorrhage may be due to trauma, a congenital aneurysm, an angiomatous tumor and disease of the cerebral arteries following infections, including bacterial endocarditis and hemorrhagic diathesis There is nothing to indicate that this child had received a head injury or that there was a hemorrhagic diathesis The spinal-fluid picture was hardly consistent with that of bacterial endocarditis Furthermore, the heart was normal

Congenital aneurysm is one of the most frequent lesions producing subarachnoid hemorrhage with symptoms of meningeal irritation, changes of awareness, fever, glycosuria and certain focal signs, such as were present in this case I have never seen a subarachnoid hemorrhage from a congenital aneurysm in an infant, however, and I did not find any case reported in the literature Our choice, then, seems to be limited to an angiomatous malformation or arterial disease as a result of infection This child had an infection a week before admission Throat cultures showed abundant alpha-hemolytic streptococci Infections such as diphtheria, influenza, scarlet fever and pneumonia can produce destructive changes in the smooth muscle and elastic tissue of the media of the arteries, resulting in necrosis and subsequent hemorrhage Since I have no personal experience with rare types of arterial hemorrhage, I consulted various books and found that these changes reach their maximum on the eighteenth day or later If that observation is correct, the much shorter interval between infection and hemorrhage in the case under discussion precludes this possibility Moreover, the onset of the disease probably antedated the upper respiratory infection by several months Nystagmus was noted at the age of eleven months, in addition to a habit of pounding the fists against the head, presumably indicating that the child had headaches

Was the nystagmus a manifestation of the local effect of the disease, or was it a symptom of a minor hemorrhage at that time? This question is difficult to answer. My guess is that the nystagmus was due to involvement of certain structures in the posterior fossa rather than to a minor hemorrhage. This leads us to the problem of localization of the lesion. Do the other neurologic findings point to a lesion in the posterior fossa? They are at least consistent with it. There was weakness of the right lower facial nerve which may have been due to brain-stem disease. The bilateral Babinski signs do not help in the localization at all.

In summary, I might say that subarachnoid hemorrhage from a congenital aneurysm is quite unlikely, that I hesitate to consider the possibility of a hemorrhage as the result of postinflammatory arterial changes and that the possibility of an angioma is a fairly good one, if the blood in the cerebrospinal fluid was not due to a bloody tap. Without the cerebrospinal-fluid findings one thinks of a tumor, whose type I cannot predict. As to the localization, all the evidence given to us points to a lesion in the posterior fossa. Needless to say, I expect to be wrong on all counts.

DR BUTLER I am astonished that you did not ask to see the x-ray films.

DR MICHELSEN I did not ask because they were said to be negative.

DR BUTLER Do you accept that as correct?

DR MICHELSEN I trust the X-ray Department.

DR BUTLER I should like to see the films. The reason I ask is that it is hard for me to believe that there was no separation of the sutures. Do you think that there was, Dr Schatzki?

DR RICHARD SCHATZKI No.

DR BUTLER This was a fourteen-month-old baby. You are sure that these sutures are no wider than they should be?

DR SCHATZKI I may be wrong, but I do not care to qualify the statement.

DR BUTLER The abstract of the case fails to indicate the severe state of collapse. The doctors who took care of the patient were handicapped in carrying out diagnostic and surgical procedures because they thought the child was going to die at any moment. The first neurologic note states "He will have to be studied as rapidly as possible consistent with his condition. I agree that the extreme dehydration must be treated now." Another note by the neurosurgeon reads "The child was taken to the operating room at 5:35 p.m., and while the head was being shaved, respirations ceased. The air passages were cleared. The child was intubated, and the above procedure was done with oxygen insufflation" — the "above procedure" being bilateral burr holes. One must be careful about performing a lumbar puncture in a patient like this. I question the advisability of doing a lumbar puncture in the sitting position, unless there is some excellent reason

for doing so, the reclining position appears preferable. When a lumbar puncture is performed on a child in whom one suspects increased intracranial pressure, the fluid should be removed with the greatest of care and only the minimal amount necessary for diagnostic procedures withdrawn. If evidence of increased intracranial pressure has been obtained by burr holes, it seems to me that the pressure should be reduced by ventricular tap. If desired, ventriculograms can then be obtained. Pneumoencephalograms in such patients with increased intracranial pressure are to be avoided as unduly dangerous. In this case, however, we shall learn from the pathologist's findings that there was not much that could have been done.

DR F. DENNETTE ADAMS How do you account for the high white-cell count and fever?

DR BUTLER The patient may have had some infection. The degree of dehydration alone, however, could have accounted for the elevation of the white-cell count. The dehydration, in addition to the intracranial disease, may have caused the elevated temperature.

CLINICAL DIAGNOSIS

Subdural hematoma?

DR MICHELSEN'S DIAGNOSIS

Expanding lesion in posterior fossa, type undetermined.

ANATOMICAL DIAGNOSIS

Brain tumor, probably oligodendroglioma

PATHOLOGICAL DISCUSSION

DR CHARLES S. KUBIE I agree with Dr. Michelsen that this was an unusually difficult case. I think that he did very well with the data available.

There was a soft tumor, almost gelatinous in consistency, 6 cm. in diameter, above the optic chiasm. It extended forward along the medial portions of the orbital surfaces of the frontal lobes, backward to the interpeduncular space and upward into the hypothalamus and third ventricle. The optic chiasm, olfactory lobes, tuber cinereum, a large part of the hypothalamus and the corticospinal tracts were invaded by the tumor. I should have expected serious impairment of vision. In the upper part of the tumor there was a small hemorrhage, communicating with the third ventricle, which unquestionably was the source of the blood in the spinal fluid.

We have had several other tumors in the same locality, all of which were more solid and less discrete and were composed of slender fusiform cells, apparently derived from the infundibulum. In this case the microscopic findings were quite different, and I do not know how to classify the tumor. The cells were rounded and fairly well stained, resembling

oligodendrocytes, but the gelatinous consistence of the tumor was unlike that of oligodendroglioma

DR TRACY B MALLORY Essentially, nothing was found in the rest of the body. There was a moderate degree of atelectasis of the lung, and the bronchi contained mucinous exudate, a finding that one would expect with the degree of respiratory difficulty that this child had had during life

CASE 33082

PRESENTATION OF CASE

A thirty-seven-year-old pregnant housewife entered the hospital in coma

A week before admission, during the sixth month of an apparently normal pregnancy, the patient had begun to complain of headache. Two days before admission a physician found the temperature to be 102°F. Since there was evidence of an upper respiratory infection, he ordered aspirin and phenacetin that day and again on the morning before admission, when the temperature was 100°F. The headache had increased by that time, and 15 mg of morphine was prescribed. At midnight relatives found the patient unresponsive and "stiff all over," with a temperature of 104°F and labored breathing. The family stated that she had passed little or no urine in the preceding two days, although she had taken fluids frequently. The physician injected 300,000 units of penicillin in oil before sending her to the hospital.

There had been no previous serious illness. The first pregnancy four years before admission had resulted in a miscarriage. Two years later a normal infant was born at full term.

On examination the patient was comatose, responding only to extremely painful stimuli. The pupils were markedly constricted. There was a purulent exudate in the nasal tract. The throat was red. Respirations were labored at 30 per minute. Breath sounds were diminished at the right lung base, and a few moist rales were heard low in both axillae. A soft apical systolic murmur and a Grade II systolic murmur were heard in the pulmonic area. The liver and spleen were not palpable. The uterine fundus rose to the level of the umbilicus. The fetal heart sounds were regular at a rate of 140 per minute. There was no vaginal discharge. The skin was clear, and no edema of the extremities was evident. The neck was not stiff, but the patient groaned when it was flexed. The tendon reflexes were hyperactive in the arms and in the left leg. There was no ankle clonus. The plantar reflex was equivocal on the right, and definitely extensor on the left.

The temperature was 99.8°F, the pulse 128, and the blood pressure 100 systolic, 60 diastolic.

Examination of the blood disclosed a hemoglobin of 12 gm per 100 cc and a white-cell count of 33,100, with 96 per cent neutrophils. The fasting blood sugar was 215 and the nonprotein nitrogen 22 mg per 100 cc, the carbon dioxide 16, the chloride 102 and the sodium 131.8 milliequiv per liter. The urine gave a +++ test for albumin. The sediment contained 3 to 5 white cells, rare red cells and 3 to 5 granular casts per high-power field. Thick, yellow spinal fluid was obtained by lumbar puncture. It contained 336,000 cells per cubic millimeter, with 95 per cent polymorphonuclears. Numerous gram positive lancet-shaped diplococci demonstrated on a smear were identified as Type 4 pneumococci. The same organism was grown from the blood. The spinal-fluid sugar was 16 and the protein 940 mg per 100 cc, the chloride was 112 milliequiv per liter. X-ray examination of the chest showed elevation of the right half of the diaphragm and mottled areas of increased density extending from low in the right hilus into the right costophrenic sinus. On the lateral view the right middle lobe appeared unusually dense.

Treatment consisted of intravenous and intrathecal penicillin and intravenous sulfadiazine and fluids. The spinal fluid gradually became less cloudy, and by the eleventh hospital day, it was clear and sterile, the sugar being 69 mg per 100 cc and the cell count 40 lymphocytes per cubic millimeter.

The patient's condition, however, did not correspond to the improved spinal-fluid findings. She never regained consciousness. Sulfadiazine had to be stopped twice because of oliguria and hematuria, although the urinary output never ceased completely. No rise in the nonprotein nitrogen resulted. Type 4 antipneumococcus rabbit serum injected on the third day apparently caused a rapid fall in the temperature to normal, but only a small amount of the serum was available. The temperature then ran between 99 and 101°F until the eleventh day, when it was again normal. There was some fluctuation in the lung signs, the rate and character of respirations and the depth of the coma, but at no time were the lungs free from signs of consolidation or atelectasis. On one occasion the extensor plantar response shifted from the left to the right, otherwise, there was no significant change in the neurologic signs. A male infant was born on the tenth day and lived only six hours.

On the thirteenth day the temperature began to rise, reaching 104 to 105°F, where it remained. The respirations were labored and rapid. On spinal puncture 30 cc of cloudy fluid containing 720 cells per cubic millimeter was obtained. No organisms grew from it. Terminally the count rose to 1200 cells per cubic millimeter, with 85 per cent polymorphonuclears. The patient died on the seventeenth day, having remained in coma during the entire period of hospitalization.

DIFFERENTIAL DIAGNOSIS

DR WIMAN RICHARDSON I do not usually ask questions, but there are a few that I should like to have answered in this case. The first is whether the pupils remained constricted or whether that condition can be attributed to morphine. Was the blood sugar taken before or after intravenous glucose was given? It is quite important to know whether the blood sugar was really elevated or whether the elevation was due to intravenous glucose. Is there any record of sulfonamide therapy during this period? How long after morphine was this examination done? The record indicates a considerable lapse of time, but I am not sure of that.

There is a little too much stress on the oliguria in this abstract.

The Babinski sign or plantar reflex, to my mind, is always equivocal so far as the diagnosis is concerned.

The hemoglobin was a low normal for a nonpregnant person. The blood picture, I suppose, is consistent with infection.

"At no time were the lungs free from signs of consolidation." No signs of consolidation were recorded so far as I can make out. There were diminished breath sounds and rales on one occasion, but consolidation is not mentioned.

"On one occasion the extensor plantar response shifted from the left to the right." Just like it!

A brief discussion of the symptoms is indicated. The onset of headache suggests the possibility of sinusitis. The history of the early oliguria, in spite of the adequate fluid intake, is something that must be explained. The clinical history is not suggestive of lobar pneumonia. There was a moderate acidosis, with a low carbon dioxide and a low blood sodium. I should like to ask Dr Butler at this point about the chloride of 102 milliequiv per liter. What happens to the chloride when the sodium is low? I should think that the chloride would have to be low.

DR ALLAN M. BUTLER Sodium and chloride are almost entirely independent. In plasma there are a variety of positively charged ions and a variety of negatively charged ions that exist almost totally dissociated as ions and are not combined as molecules.

DR RICHARDSON But the total has to be balanced?

DR BUTLER Yes, the total positive and negative ions must balance. In this patient the carbon dioxide was reduced from the normal of 26 to 16 milliequiv per liter. The chloride was normal. The sodium was somewhat low, but it is hard to say how low, because there is a variation in the normal sodium concentration of 136 to 147 milliequiv per liter by the method used in this case, just as there is a variation in the normal chloride from 100 to 107 milliequiv per liter. The carbon dioxide may

have been low because there was hyperventilation with the meningitis. Such hyperventilation would also tend to lower the sodium and to raise the chloride. Also, the ketosis of starvation might tend to lower the carbon dioxide. Thus, the changes in electrolyte concentrations are consistent.

The thing that is important is to use this case as a plea to stop asking the laboratory to test the spinal-fluid chloride when there is no possible information to be obtained from it. Unless one is dealing with a possible diagnosis of tuberculous meningitis, there is no rhyme or reason for requesting that determination, and even in cases of tuberculous meningitis, the chloride is of no help unless a simultaneous serum chloride is tested.

DR RICHARDSON I shall call attention to the lack of rise in the nonprotein nitrogen. And no dysuria was reported at any time.

With some diffidence, I am going to criticize the treatment. I do not like to do this as a rule, because hindsight is easier than foresight. I wonder, however, whether it was justifiable, in spite of the severity of the infection, to use the sulfonamides in the face of a marked oliguria. I should like to ask what the output was. And I should like to know whether or not the elevated blood sugar was important. I have in mind the possibility that the patient had moderate diabetes, which might have led to certain diseases. According to this chart that Dr Mallory has shown me, the output during the middle of the course of the illness was fairly good.

DR TRACY B. MALLORY I think that the oliguria followed the sulfonamide treatment rather than preceded it.

DR RICHARDSON The output was over 1500 cc, and one might be justified in giving sulfonamide in such a desperately sick patient. Another criticism is that there was a distinct likelihood of intracranial pressure and of cerebral disease in this patient, but from the record the possibility does not seem to have been investigated. There was undoubtedly some good reason, however. I think that there were lesions in the spinal canal and brain, possibly in the kidneys and possibly in the lungs. In the spinal canal we know that there was an acute purulent meningitis, due to the Type 4 pneumococcus. Was there disease in the brain? Pneumococcal meningitis could have resulted in obstruction at the foramen of the fourth ventricle — what do you call it, Dr Kubik?

DR CHARLES S. KUBIK The foramen of Magendie and Luschka.

DR RICHARDSON Obstruction can occur at that point and does so in certain types of meningitis, with a resulting internal hydrocephalus. Constricted pupils may, I believe, point to midbrain lesions. Dr Kubik will check me on that. This is the only evidence I find of localization of a brain lesion. On the other hand there is a distinct suggestion of sinusitis

in this case, and it is quite probable that the coma, which was the presenting symptom and never cleared, was due to a brain lesion, with increased intracranial pressure. The question is, Just what type of obstruction due to meningitis was this? Was it caused by a lesion pressing at the base of the brain? There is a definite possibility that this patient had a localized lesion. I suspect that the trouble started with ethmoiditis or infection in the sinuses, including the ethmoid, and I think that there might have been a localized abscess in the brain. There is little evidence on which to base such a diagnosis, except that the patient did not get well.

What about the kidneys, which seem to have been involved? In pregnancy the lesion described as diffuse cortical necrosis may occur. Terminally, there does not seem to be enough renal failure to allow for such a diagnosis. Recently, Robbins, Mallory and Kinney* described a disease known as necrotizing papillitis. Their cases occurred in conjunction with a severe infection in diabetic patients, and were not necessarily associated with pregnancy. One might consider glomerulonephritis as a result of infection, but, again, the picture in the case under discussion does not seem to have been that of glomerulonephritis. I think that the kidneys will show multiple abscesses, as a result of a septicemia due to the pneumococcus. There is no evidence of pyuria to go with multiple infections in the kidneys, but this possibility must be considered. Finally, it must be determined whether this patient had a sulfonamide nephrosis, with some renal failure. All the conditions that I have mentioned are questionable. I do not know how to make a definite statement.

What about the lung? I do not believe that there was any disease in the lung.

DR RICHARD SCHATZKI: There is one more film taken in bed in which there is definite abnormality in the right middle lobe, which is markedly decreased in size. There is atelectasis in the middle lobe and, in addition, disease in the lower lobe that also looks like atelectasis.

DR RICHARDSON: I am going to forget about the lungs. I think that they were "wet." I do not see clinical or x-ray evidence of pneumonia. There could have been a lesion to account for metastases to the brain or for meningitis. I do not see it. I say that this patient had a meningitis due to a Type 4 pneumococcus. I am sure of that. I believe that the cerebral lesion was an abscess, probably arising from a sinusitis. The kidneys will show small abscesses and possibly a sulfonamide nephrosis.

DR BUTLER: So far as the therapy is concerned, I should argue that it was correct to use the sulfonamides and penicillin. In administering sulfadiazine one ought, of course, to see to it that everything is done to maintain a proper urine volume. I do not

believe that a urine volume of 1500 cc must be present before one is justified in giving sulfonamides to such a patient as this. As I look at the chart of the urine output, the treatment appears justified.

DR MALLORY: The sulfonamides were given in two periods. The urinary output dropped, and treatment was stopped, it went up, and the sulfonamides were tried again.

DR RICHARDSON: I am sure that there is going to be something wrong with the kidneys.

CLINICAL DIAGNOSES

Meningitis³ due to Type 4 pneumococcus
Bronchopneumonia

DR RICHARDSON'S DIAGNOSES

Acute ethmoiditis
Acute meningitis (Type 4 pneumococcus)
Brain abscess
Multiple renal abscesses
Sulfonamide nephrosis?

ANATOMICAL DIAGNOSES

Acute sinusitis, left ethmoid and sphenoid
Bacterial endocarditis, mitral valve (Type 4 pneumococcus)
Multiple infarcts and abscesses of brain
Meningitis, pneumococcal, healing
Infarct of heart
Infarct of left kidney, healing
Bronchopneumonia, slight.

PATHOLOGICAL DISCUSSION

DR MALLORY: The primary lesion at autopsy was not mentioned by Dr Richardson, although he foretold many of the complications. It was an acute bacterial endocarditis of the mitral valve consequent to a pneumococcal septicemia that the patient had had at the start of the illness. Dr Richardson was correct in suspecting underlying sinusitis. There was severe chronic infection of the left ethmoid and sphenoid sinuses. There was little in the lung other than considerable atelectasis and a few small patches of terminal pneumonia. The long coma was explained when we examined the brain — there was almost no anatomical evidence of persisting meningitis, but on section innumerable areas of softening throughout the white matter were found, many of which seemed primarily to be infarction but a few of which contained enough leukocytes to be classified as abscesses. There had also been an embolism of the coronary arteries, and a considerable area of infarction was found. The kidneys were perfectly normal except for one small, almost healed infarct.

DR RICHARDSON: I do not see why you call bacterial endocarditis the primary lesion. I should think that it was secondary to the sinus infection, with septicemia, and then an implantation.

DR MALLORY: Yes, the sinuses were the portal of entry of the infection, but the endocarditis and the consequent multiple septic emboli to the brain were the basic lesions accounting for death.

*Robbins, S. L., Mallory, G. K. and Kinney, T. D. Necrotizing renal papillitis form of acute pyelonephritis. *New Eng J Med* 235: 885-893 1946

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

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United States (medical students \$5.50 per year) Canada \$7.00 per year
(Boston funds) \$8.50 per year for all foreign countries belonging to the
Postal Union.

MATERIAL should be received not later than noon on Thursday, two
weeks before date of publication

THE JOURNAL does not hold itself responsible for statements made by any
contributor

COMMUNICATIONS should be addressed to the *New England Journal of
Medicine*, 8 Fenway, Boston 15, Massachusetts

THE RED CROSS. A HEALTH-PROMOTING AGENCY

THE opening rally of the 1947 Greater Boston Red Cross Fund will be held on February 27 at Symphony Hall. From then through March 26 all residents and workers of Greater Boston are being asked to contribute to the \$1,280,000 that is Greater Boston's part of the \$60,000,000 to be raised nationally by this great humanitarian organization. Of all money contributed, 75 per cent will go to serve veterans, servicemen and their families. The remainder will go for those regular Red Cross services of disaster relief, water safety, first aid, nutrition, nursing, transportation and other health and educational activities.

The American Red Cross is carrying a heavy load of responsibilities accumulated during the war. It

is helping to fulfill the many promises made by grateful citizens to their servicemen by aiding veterans both in hospitals and in their homes. The Army, Navy and Veterans Administration have provided for meeting the basic needs of the men and women in their installations. Situations arise, however, when there is need for equipment and supplies that cannot be obtained through official sources. As physicians are the first to realize, recovery from both physical and mental illnesses often depends on more than medicine or the best surgical skill. At the request of regular hospital personnel, the Red Cross provides carefully trained workers to help speed return to health and usefulness. It also furnishes supplies and equipment for making recovery and rehabilitation quicker and easier.

Despite continued nursing shortages nationally, 852 nurses served under Red Cross direction in seventy-four disasters in thirty-six states during 1945-1946. Sixteen floods in as many states, sixteen tornadoes in fifteen states, fourteen epidemics in thirteen states and thirteen major fires in nine states led the list of fiscal catastrophes. Disasters with proportionately fewer nursing needs were train wrecks, explosions, hurricanes and bus and other accidents.

The Red Cross also carried on a home-nursing program to promote better family and community health. Such training includes instruction in personal health, the care of mother and baby and the control of communicable diseases in the home and community. The objective is to train one person in every home to take care of minor illnesses under the doctor's orders and to realize that a minor illness may become a major illness unless proper nursing and medical care are given.

Red Cross public-health nursing services have been established in rural areas and small towns where other local health agencies had no plans or possibilities for organizing such a service. These public-health nursing services are established only after a careful study of community needs, consultation with state and local departments of health and the approval of the Area Red Cross office.

Red Cross first-aid training develops the knowledge and skill necessary for the care of the victim of an accident or sudden illness until the services of

a physician can be obtained. It has often meant the difference between life and death, between temporary and permanent disability or between rapid recovery and long hospitalization. It is also an important part of industrial safety programs, and reports from throughout the Nation indicate that such training frequently curtails the number of lost-time accidents by as much as 50 per cent.

The Red Cross is a health-promoting agency — in the home, in the hospital, on the highway. It gives food to those in other countries left starving by war and disaster. It teaches food preservation and good nutrition to the housewives of this country. Its financial assistance helps many a veteran's or serviceman's family when the need arises or over a temporary period until a Government claim or other plan can be established. It also brings comfort, nursing service and help to veterans, servicemen and civilians in hospitals throughout the country. In other words, the Red Cross gives service and help wherever there is need. Physicians should continue to support this great humanitarian organization!

Q FEVER

DURING the past two years, while the search continued for the agent or agents that are responsible for the disease known as "virus pneumonia," considerable information has accumulated concerning the occurrence of the specific rickettsial disease Q fever as a cause of some severe types of atypical pneumonia. Most of the new information regarding this disease was collected by workers in Army hospitals and laboratories and has been published only recently. The identity of the agent and some aspects of its epidemiology and pathogenicity have come to light during the last decade.

In 1937, Derrick¹ described an influenza-like infection occurring among meat workers that had come into prominence since 1935 in Queensland, Australia, he called the disease "Q fever." The causative agent was isolated by the intraperitoneal injection of guinea pigs with the blood and urine obtained from patients during the acute stage of the disease. The agent was studied in detail by Burnet and Freeman,² who showed it to be a filter-passing rickettsia. They showed that specific antibodies

developed toward the end of the second week of illness and could be demonstrated by the agglutination of suitable suspensions of the rickettsia. Infection with the rickettsia was found to be widespread in a native rodent, the bandicoot, which served as a reservoir, with certain ticks acting as vectors. Forest workers and cattle were infected directly by infected ticks, and slaughterhouse workers were thought to be infected by the inhalation of dried feces of ticks infected from the cattle.³ Pneumonia was not recognized as a feature of Q fever in the Australian cases. The organism was named *Rickettsia burneti*.

An agent similar to *R. burneti* was isolated at about the same time by workers in the Rocky Mountain Laboratory of the United States Public Health Service from ticks collected in Montana and Wyoming.⁴ A disease corresponding to Australian Q fever is known to occur in this area, and serologic evidence of infection with the agent was found in persons over a large area of the United States, ranging from Nebraska to Texas and Washington.⁵ In 1940, an outbreak of pneumonitis due to the organism of Q fever occurred at the National Institute of Health in Bethesda, Maryland.⁶

The studies made by the Army workers have been recently reported in detail.⁷ During the winter of 1944-1945 outbreaks of severe atypical pneumonia occurred among British troops stationed in the Mediterranean area and also among American military units in Corsica. The disease differed in some important respects from the atypical pneumonia that was prevalent in the United States and Great Britain. It seemed to be sharply limited to particular units and areas and was characterized by a high attack rate, — up to 50 per cent, — and there was no associated increase in cases of minor respiratory illnesses. The clinical and epidemiologic findings were readily corroborated when an opportunity arose to investigate an outbreak among the members of a British parachute regiment who had acquired the infection in Athens. Although the studies in that outfit began when the outbreak was subsiding, it was possible to identify its nature in retrospect by the laboratory examination of serum specimens from patients.

Four similar outbreaks were investigated among American military units stationed in Italy near Florence and Bologna. The rickettsia of Q fever was isolated from the blood of some of the patients in these outbreaks and was shown to be the cause of the outbreaks. At the same time it was demonstrated serologically that about three fourths of the sporadic cases of atypical pneumonia in the same region were, in fact, cases of Q fever. These laboratory studies were carried out chiefly in the Fifteenth Medical General Laboratory which was serving this area.

At about the same time it was also learned that an outbreak of a severe influenza-like infection associated with atypical pneumonia had occurred during the preceding winter in Athens. The Germans, who seemed to be more severely affected than the natives, called it the "Balkan gripe." Dr J. Caminopetros, of the Pasteur Institute of Greece, was able to establish a transmissible febrile illness in guinea pigs by the inoculation of blood from a patient obtained during the acute stage of the disease. One of these guinea pigs was later brought to the laboratories of the Commission on Acute Respiratory Disease at Fort Bragg, North Carolina, where the rickettsia of Q fever was isolated and identified.

During May and June, 1945, other outbreaks occurred among certain units that were being returned to the United States from southern Italy. One of these was studied by the medical officers at Camp Patrick Henry, Virginia, and the etiologic and epidemiologic aspects were investigated by the Commission on Acute Respiratory Diseases. The cause of this outbreak was identified as the Balkan-gripe type of *R. burneti*.

Outbreaks of severe atypical pneumonia occurred among the personnel of the two laboratories in which these investigations were being carried out. The one in the Fifteenth Medical General Laboratory was shown by isolation of the agent and by serologic studies, to have been due to the Italian strain of *R. burneti*, and similar studies in the Fort Bragg laboratory indicated that the infections there were caused by the Balkan strain. There were no deaths among these cases.

Another possible focus of Q fever was suggested by the report of a case of atypical pneumonia in a

military hospital in Panama. Serologic studies of the blood of the patient and of the agent that was isolated from the blood indicated that the disease was caused by a strain of the American type of Q fever. The patient had been in Panama for several months prior to his illness.

A preliminary report has also appeared about an outbreak of Q fever that occurred in Amarillo, Texas, in May, 1946.⁸ There were more than 40 cases. Most of them occurred in men who were employees of a stockyard and meat-packing company, but some were observed among railroad workers and others around the stockyards. There were 2 deaths in this outbreak.

The strains of *R. burneti* isolated from the various outbreaks have many characteristics in common. Antigenic differences among these strains have been partially worked out by investigators at the National Institute of Health. These differences suggest that Q fever may be more prevalent in the United States than was previously suspected and that cases may have been missed because of the improper selection of strains for the serologic tests.

REFERENCES

1. Derrick, E. H. "Q" fever: new fever entity: clinical features, diagnosis and laboratory investigation. *M. J. Australia* 2:281-295, 1937.
2. Burnet, F. M. and Freeman, M. Experimental studies on virus of "Q" fever. *M. J. Australia* 2:299-305, 1937.
3. Derrick, E. H. Epidemiology of Q fever. *J. Hyg.* 43:357-361, 1944.
4. Davis, G. E. and Cox, H. R. Filter passing infectious agent isolated from ticks. I. Isolation from *Dermacentor andersoni*; reactions in animals and filtration experiments. *Pub. Health Rep.* 53:2259-2267, 1938.
5. Cox, H. R. Rickettsia diaponica and American Q fever. *Am. J. Trop. Med.* 20:463-469, 1940.
6. Hornbrook, J. W. and Nelson, K. R. Institutional outbreak of pneumonitis. I. Epidemiological and clinical studies. *Pub. Health Rep.* 55:1936-1944, 1940.
7. Robbins, F. C. and others. Q fever: series of twelve papers. *Am. J. Hyg.* 44:1-182, 1946.
8. Irons, J. V., Topping, N. H., Shepard, C. C., and Cox, H. R. Outbreak of Q fever in United States. *Pub. Health Rep.* 61:784, 1946.

MASSACHUSETTS MEDICAL SOCIETY

TREASURER'S OFFICE

All members should be reminded that the proportion of the refund returned to each district society is based on the number of dues paid by March 1 in that district, and also that the names of members who have not paid their dues by March 1 are automatically removed from the mailing list of the *Journal* until such dues are paid.

ELIOT HUBBARD, JR., *Treasurer*

DEATH

JOHNSON — Herbert L. Johnson, M.D., of Hadley, died January 22. He was in his eighty-eighth year. Dr. Johnson received his degree from Bowdoin Medical School in 1884.

POSTGRADUATE LECTURE COURSE

The review Postgraduate Lecture Course, which has been arranged by the Committee on Postgraduate Medical Education, Massachusetts Medical Society, in co-operation with the Massachusetts Department of Public Health, will begin on March 3. The meetings will be held at Sanders Theater in Memorial Hall, Harvard University, Cambridge. These lectures are primarily designed for general practitioners, but medical officers, hospital interns and residents, and postgraduate and undergraduate medical students are cordially invited to attend. Recent progress in medicine will be discussed, and the speakers have been urged to present their subjects in a simple and direct manner and to emphasize diagnosis and treatment from the point of view of the physician in general practice.

All those who plan to attend but have not enrolled should do so immediately by either returning the post card recently forwarded to all physicians in Massachusetts or addressing a post card or letter directly to the Postgraduate Lecture Course Committee, Massachusetts Medical Society, 8 Fenway, Boston 15.

The detailed program for the course is as follows

REVIEW LECTURE COURSE

Monday, March 3 5 30-5 45 **OPENING REMARKS** Dwight O'Hara president, Massachusetts Medical Society, dean, Tufts College Medical School

MEDICAL ASPECTS OF ATOMIC WARFARE *Chairmen* Shields Warren and Stafford L. Warren

5 45-6 45 Medical Implications of the Bikini Experiments. Capt. George M. Lyon (MC), USNR, assistant to the Surgeon General, Navy Department Washington, D. C., representative, Bureau of Medicine and Surgery, U. S. N., Joint Task Force One

7 00-7 30 Buffet Supper

7 30-8 00 The Pathology of Atomic-Bomb Injuries Shields Warren formerly, director of medical research, Bikini Project, pathologist, New England Deaconess and New England Baptist hospitals

8 00-8 30 General Aspects of Atomic Energy Stafford L. Warren formerly, medical director, Manhattan Project, professor of radiology, University of Rochester Medical School, Rochester, New York

8 30-9 00 Motion pictures of Bikini Experiment

Wednesday, March 5 INFECTIOUS DISEASES *Chairmen* Maxwell Finland and Conrad Wesselhoft

3 00-3 35 Rubella and Congenital Deformities — The present problem Conrad Wesselhoft physician-in-chief, Haynes Memorial, Massachusetts Memorial Hospitals, clinical professor of communicable diseases, Harvard Medical School and Boston University School of Medicine

3 35-4 10 Pneumonias Maxwell Finland chief, Fourth Medical Service, and associate physician, Thorndike Memorial, Boston City Hospital, assistant professor of medicine, Harvard Medical School

4 10-4 45 Meningitis Louis Weinstein visiting physician, Haynes Memorial, Massachusetts Memorial Hospitals, assistant professor of medicine, Boston University School of Medicine

4 45-5 10 Intermission

5 50-5 25 Use of Gamma Globulin Charles A. Janeway professor of pediatrics, Harvard Medical School, chief, Medical Service, Children's Hospital

5 25-6 00 Prophylactic Inoculations Geoffrey Edsall instructor in bacteriology and applied anatomy, Harvard Medical School, assistant director, Division of Biologic Laboratories, Massachusetts Department of Public Health

Monday, March 10 PART I CHEST DISEASE *Chairmen* Theodore L. Badger and Reeve H. Betts

5 30-6 00 The Role of Surgical Exploration in the Diagnosis and Treatment of Intrathoracic Lesions Reeve H. Betts assistant professor of surgery, Tufts College Medical School

6 00-6 30 The Value of Streptomycin and BCG in the Treatment and Prevention of Tuberculosis. Lowrey F. Davenport instructor in medicine, Harvard Medical School

6 30-7 00 The Management of Suppurative Diseases of the Lung John W. Strieder associate professor of surgery, Boston University School of Medicine, chief, Thoracic Surgery, Boston City Hospital, visiting surgeon in charge of thoracic surgery, Massachusetts Memorial Hospitals

7 00-7 30 Buffet Supper

PART II NEUROSURGICAL DISEASE *Chairmen* Gilbert Horrax and James C. White

7 30-8 00 The Neurosurgical Treatment of Pain James C. White assistant professor of surgery, Harvard Medical School, chief of neurosurgical service, Massachusetts General Hospital

8 00-8 30 The Treatment of Spinal-Cord Injury Donald Munro associate professor of neurosurgery, Boston University School of Medicine, assistant professor of neurosurgery, Harvard Medical School, surgeon-in-chief and Head of Department of Neurosurgery, Boston City Hospital

8 30-9 00 The Diagnosis and Treatment of Brain Tumors Gilbert Horrax chief of Department of Neurosurgery, Lahey Clinic, neurosurgeon to New England Deaconess and New England Baptist hospitals

Wednesday, March 12 INFANTILE PARALYSIS AND BACK PAIN *Chairmen* William T. Green and Arthur A. Thibodeau

3 00-3 25 Epidemiology of Infantile Paralysis Charles A. Janeway professor of pediatrics, Harvard Medical School, chief, Medical Service, Children's Hospital

3 25-3 50 Diagnosis and Early Care of Infantile Paralysis Thomas Gucker assistant in orthopedic surgery, Children's Hospital

3 50-4 15 The Treatment of Infantile Paralysis during Convalescence David S. Grice junior attending orthopedic surgeon, Children's Hospital and Peter Bent Brigham Hospital, assistant in Department of Orthopedics, Harvard Medical School, assistant director, Massachusetts Infantile Paralysis Clinics

4 15-4 30 The Chronic Stage of Infantile Paralysis — Rehabilitation William T. Green assistant professor of orthopedics, Harvard Medical School, orthopedic surgeon-in-chief, Children's Hospital

4 30-4 40 Intermission

4 40-5 05 Body Mechanics, Examination of the Back, Postural Back Ache James W. Toumey orthopedic surgeon, Lahey Clinic, New England Baptist and New England Deaconess hospitals

5 05-5 30 Acute Back Strain and Other Causes of Back Pain Arthur A. Thibodeau instructor in orthopedics, Tufts College Medical School

5 30-6 00 Sciatica and Rupture of Intervertebral Disk Joseph S. Barr clinical professor of orthopedic surgery, Harvard Medical School, chief of Orthopedic Staff, Massachusetts General Hospital

Monday, March 17 MINOR SURGERY AND SURGICAL SHOCK
Chairmen Augustus Thorndike and C. Stuart Welch

5 30-6 15 **Injuries of the Hand** Examination, diagnosis and early treatment Henry C. Marble assistant in surgery, Harvard Medical School, visiting surgeon, Massachusetts General Hospital surgeon-in-chief, Chelsea Memorial Hospital

6 15-7 00 **Infections of the Skin — Pustular Acne, Furunculosis and Carbuncles** Joseph Tartakoff assistant professor of surgery, Tufts College Medical School, assistant visiting surgeon, Boston City Hospital

7 00-7 30 **Buffet Supper**

7 30-8 00 **Sprains, Strains and Contusions Pathology and treatment** Thomas B. Quigley associate in surgery, Harvard Medical School and Peter Bent Brigham Hospital

8 00-8 30 **Surgical Shock** John E. Dunphy associate in surgery, Harvard Medical School, visiting surgeon, Peter Bent Brigham Hospital

8 30-9 00 **Burns of the Hand** Early and late treatment Melvin F. White assistant professor of surgery, Tufts College Medical School, visiting surgeon, St. Elizabeth's Hospital, plastic surgeon, Tumor and Surgical Departments, Boston Dispensary

Wednesday, March 19 ANESTHESIA AND ITS COMPLICATIONS
Chairmen Henry K. Beecher and Morris J. Nicholson

3 00-3 40 **Current Trends in the Use of General Anesthesia** M. Gene Black anesthetist, Massachusetts Memorial Hospitals, instructor in anesthesiology, Boston University School of Medicine

3 40-4 20 **Management of the Patient under Spinal Anesthesia** Leo V. Hand anesthetist, New England Deaconess Hospital

4 20-4 40 **Intermission**

4 40-5 20 **Postanesthetic Complications** Morris J. Nicholson Department of Anesthesiology, Lahey Clinic, anesthetist, New England Deaconess and New England Baptist hospitals

5 20-6 00 **Evaluation and Care of the Patient in Shock** Henry K. Beecher anesthetist-in-chief, Massachusetts General Hospital, Henry I. Dorr Professor of Research in Anesthesia, Harvard Medical School

Monday, March 24 ENDOCRINOLOGY, INCLUDING DIABETES
Chairmen Richard P. Stetson and George W. Thorn

5 30-6 00 **Carbohydrate Metabolism** Recent concepts Richard P. Stetson associate in medicine, Harvard Medical School, assistant visiting physician, Boston City Hospital

6 00-6 30 **Diabetes Mellitus** Degenerative complications Alexander Marble instructor in medicine, Harvard Medical School, physician, New England Deaconess Hospital

6 30-7 00 **Adrenal Insufficiency** Diagnostic criteria George W. Thorn Hersey Professor of Theory and Practice of Physic, Harvard Medical School, physician-in-chief, Peter Bent Brigham Hospital

7 00-7 30 **Buffet Supper**

7 30-8 00 **Thyrotoxicosis — Pathologic Physiology** Rulon W. Rawson associate in medicine, Harvard Medical School, assistant physician, Massachusetts General Hospital

8 00-8 30 **Thyrotoxicosis — Evaluation of Treatment with Thiouracil Compounds** Robert H. Williams associate in medicine, Harvard Medical School, junior visiting physician, Boston City Hospital

8 30-9 00 **Postmenopausal Osteoporosis** Fuller Albright associate professor of medicine, Harvard Medical School, physician, Massachusetts General Hospital

Wednesday, March 26 GYNECOLOGY AND STERILITY
Chairmen Samuel R. Meaker and Fred A. Simmons

3 00-3 25 **Management of Dysmenorrhea** Somers H. Sturgis assistant surgeon, Massachusetts General Hospital, assistant in gynecology, Harvard Medical School

3 25-3 50 **Habitual Abortion** Arthur T. Hertig pathologist, Boston Living-in Hospital and Free Hospital for Women, assistant professor of pathology and obstetrics, Harvard Medical School

3 50-4 15 **Ovulation Timing** Fred A. Simmons assistant surgeon, Massachusetts General Hospital and Free Hospital for Women, assistant in gynecology, Harvard Medical School

4 15-4 30 **Intermission**

4 30-5 00 **Depressed Respiratory Metabolism and Low Fertility** Samuel R. Meaker gynecologist, Massachusetts Memorial Hospitals, professor of gynecology, Boston University School of Medicine

5 00-5 30 **Ovarian Hormone Therapy** Max Davis obstetrician and gynecologist, Massachusetts Memorial Hospitals, assistant professor of obstetrics and gynecology, Boston University School of Medicine

5 30-6 00 **Findings and Results in a Series of Sterility Cases** A. Seymour Parker, Jr. physician, Medical Department, Lahey Clinic

Monday, March 31 OBSTETRICS
Chairmen Roy J. Heffernan and Frederick C. Irving

5 30-5 50 **Diet in Pregnancy** Bertha L. Burke assistant professor of maternal and child nutrition, Harvard School of Public Health

5 50-6 20 **The Rh Factor** Louis K. Diamond assistant professor of pediatrics, Harvard Medical School, visiting physician, Children's Hospital

6 20-6 40 **New Developments in Prenatal Care** Charles L. Sullivan assistant obstetrician St. Elizabeth's Hospital and Massachusetts General Hospital

6 40-7 00 **Induction of Labor** Roy J. Heffernan visiting obstetrician and gynecologist, Carver Hospital, consulting obstetrician and gynecologist, Faulkner Hospital and St. Margaret's Hospital

7 00-7 30 **Buffet Supper**

7 30-7 50 **The Use of X-Ray in Obstetrics** Daniel J. McSweeney assistant professor of obstetrics, Boston University School of Medicine and Tufts College Medical School, visiting obstetrician, Boston City Hospital and St. Margaret's Hospital

7 50-8 10 **The Fetus during Labor** Charles L. Sullivan

8 10-8 30 **Extrauterine Pregnancy** Daniel J. McSweeney

8 30-8 50 **Indications for Forceps Delivery** Roy J. Heffernan

Wednesday, April 2 GASTROENTEROLOGY
Chairmen Franz J. Ingelfinger and Chester M. Jones

3 00-3 25 **Procedures in Diagnosis and Management of Peptic Ulcer** Franz J. Ingelfinger associate professor of medicine, Boston University School of Medicine, chief, Gastrointestinal Outpatient Department, Massachusetts Memorial Hospitals, member of staff, Robert Dawson Evans Memorial Hospital

3 25-3 50 **Medical Management of Peptic Ulcer** Sara M. Jordan director of gastroenterology, Lahey Clinic, physician, New England Baptist and New England Deaconess hospitals

3 50-4 15 **Surgical Management of Peptic Ulcer** Francis D Moore associate in surgery, Harvard Medical School, assistant surgeon, Massachusetts General Hospital

4 15-4 30 **Intermission**

4 30-5 05 **Diagnostic and Medical Measures Pertinent to the Problem of Painless Jaundice** Chester M Jones clinical professor of medicine, Harvard Medical School, physician, Massachusetts General Hospital

5 05-5 40 **Surgical Measures in Relation to Painless Jaundice** Reginald H Smithwick professor of surgery, Boston University School of Medicine, surgeon-in-chief, Massachusetts Memorial Hospitals, member of board of consultants, Massachusetts General Hospital

5 40-6 00 **Discussion**

Monday, April 7. PART I OFFICE PROCEDURES IN ANORECTAL DISEASE *Chairmen* E Parker Hayden and Neil W Swinton

5 30-5 45 **Differential Diagnosis of Rectal Bleeding and Methods of Rectal and Colon Examinations** E Parker Hayden chief, Proctologic Clinic, and assistant visiting surgeon, Massachusetts General Hospital

5 45-6 00 **Hemorrhoids** Roy E Mabrey assistant surgeon, Massachusetts General Hospital

6 00-6 10 **Anal Fissure** Roy E Mabrey

6 10-6 25 **Anorectal Abscess and Fistula** E Parker Hayden

6 25-6 40 **Premalignant Lesions of the Rectum and Colon** Neil W Swinton surgeon, Lahey Clinic, New England Deaconess and New England Baptist hospitals

6 40-7 00 **Anal Pruritus** Neil W Swinton

7 00-7 30 **Buffet Supper**

PART II RADIATION THERAPY *Chairmen* Joseph H Marks and Samuel A Robins

7 30-7 45 **Contact Therapy of Superficial Lesions** Bernard E LeVine radiation therapist, Beth Israel Hospital

7 45-8 00 **Hodgkin's Disease** Hugh F Hare director, Department of Radiology, Lahey Clinic

8 00-8 15 **Fibroids and Menorrhagia** Samuel A Robins professor of radiology, Tufts College Medical School, chief radiologist, Beth Israel Hospital and Evangeline Booth Hospital

8 15-8 30 **Carcinoma of the Cervix** Laurence L Robbins roentgenologist, Massachusetts General Hospital

8 30-8 45 **Carcinoma of the Ovary** Joseph H Marks instructor in radiology, Harvard Medical School, radiologist, New England Deaconess and Palmer Memorial hospitals

8 45-9 00 **Discussion**

Wednesday, April 9 DISEASES OF BLOOD AND LYMPH NODES *Chairmen* William Dameshek and Thomas H Ham

3 00-3 30 **Diagnosis of Anemia** Thomas H Ham assistant professor of medicine, Harvard Medical School, associate physician, Thorndike Memorial, and junior visiting physician, Boston City Hospital

3 30-4 00 **Treatment of the Anemias** Maurice B Strauss chief of medical service, Cushing General Hospital, Framingham

4 00-4 35 **Diagnosis and Treatment of Disorders of the Spleen** William Dameshek professor of clinical medicine, Tufts College Medical School, hematologist, Pratt Diagnostic Hospital, chief, Blood Clinic, Boston Dispensary

4 35-4 45 **Intermission**

4 45-5 15 **Treatment of Leukemia** Henry Jackson, Jr associate physician, Thorndike Memorial, Boston City Hospital, assistant professor of medicine, Harvard Medical School

5 15-5 45 **Transfusion Therapy** Charles P Emerson assistant professor of medicine, Boston University School of Medicine, member of staff, Massachusetts and Evans Memorial hospitals

5 45-6 00 **Discussion**

Monday, April 14 THE PREVENTION OF VENOUS THROMBOSIS AND PULMONARY EMBOLUS *Chairmen* Arthur W Allen, James A Evans and John Homans

5 30-6 00 **Clinical Features of Pulmonary Embolism** Lewis Dexter assistant in medicine, Harvard Medical School, senior associate in medicine, Peter Bent Brigham Hospital

6 00-6 30 **Experiences with Heparin in Pitkin's Menstruum Combined with Dicumarol in the Treatment of Venous Thrombosis** James A Evans physician, Lahey Clinic, physician, New England Baptist and New England Deaconess hospitals

6 30-7 00 **Anticoagulant Drugs versus Vein Ligation in the Treatment of Thrombophlebitis at the Beth Israel Hospital** Arnold Starr junior visiting surgeon, Beth Israel Hospital

7 00-7 30 **Buffet Supper**

7 30-8 00 **Three-year Study of Rest, Exercise and Early Ambulation Relative to Venous Thrombosis** Analysis of 2000 consecutive cases James C McCann surgeon, St Vincent's Hospital, Worcester.

8 00-8 30 **Prophylactic Femoral-Vein Division at the Massachusetts General Hospital** Robert R Linton visiting surgeon and chief, Peripheral Vascular Clinic, Massachusetts General Hospital, associate in surgery, Harvard Medical School

8 30-9 00 **The Prophylactic Use of Dicumarol in Gynecology** George Van S Smith professor of gynecology, Harvard Medical School, chief, Free Hospital for Women

Wednesday, April 16 PART I KIDNEY DISEASE *Chairmen* Reginald Fitz and W Richard Ohler

3 00-3 30 **Diagnosis of Renal Disease** Laurence B Ellis associate in medicine, Harvard Medical School, assistant visiting physician, Boston City Hospital

3 30-4 30 **Treatment of Renal Disease** Reginald Fitz lecturer on the history of medicine, Harvard Medical School, consulting physician, Peter Bent Brigham Hospital, and W Richard Ohler, assistant professor of medicine, Harvard Medical School, chief, Second Medical Service, Boston City Hospital

4 30-4 35 **Intermission**

PART II HYPERTENSION *Chairmen* Robert S Palmer and Reginald H Smithwick

4 35-5 00 **The Heart in Hypertension** Paul D White clinical professor of medicine, Harvard Medical School, physician, Massachusetts General Hospital

5 00-5 30 **The Value of Various Therapeutic Measures in the Management of Hypertension and Hypertensive Cardiovascular Disease** Robert S Palmer associate physician, Massachusetts General Hospital, consultant, Massachusetts Eye and Ear Infirmary

5 30-6 00 **Surgical Measures in Hypertensive Patients** Reginald H Smithwick professor of surgery, Boston University School of Medicine, surgeon-in-chief, Massachusetts Memorial Hospitals

Monday, April 21. CARDIOVASCULAR DISEASES *Chairmen* Samuel A Levine and Howard B Sprague

5 30-6 00 **Pericarditis** Howard B Sprague instructor in medicine, Harvard Medical School, associate physician, Massachusetts General Hospital, chief of medicine, House of the Good Samaritan

6 00-6 30 **The Diagnosis of Coronary-Artery Disease** James M Faulkner professor of medicine, Tufts College Medical School

6 30-7 00 **The Treatment of Cardiac Emergencies** Paul D White clinical professor of medicine, Harvard Medical School, physician, Massachusetts General Hospital

7 00-7 30 **Buffet Supper**

7 30-8 00 **The Clinical Features of Patent Ductus Arteriosus** Samuel A Levine assistant professor of medicine, Harvard Medical School, physician, Peter Bent Brigham Hospital

8 00-8 30 **The Heart in Acute Infections** Charles A Janeway professor of pediatrics, Harvard Medical School

8 30-9 00 **The Treatment of Subacute Bacterial Endocarditis** Chester S Keefer professor of medicine, Boston University School of Medicine, director, Evans Memorial, Massachusetts Memorial Hospitals

Wednesday, April 23 **PEDIATRICS** Chairmen Stewart H Clifford and Richard C Tefit, Jr

3 00-3 45 **Influenza Meningitis Diagnosis and treatment** John A V Davies assistant professor of pediatrics, Harvard Medical School

3 45-4 30 **Factors Influencing the Growth and Development of the Fetus** Clement A Smith assistant professor of pediatrics, Harvard Medical School

4 30-4 40 **Intermission**

4 40-5 15 **Influence of Disease on the Growth and Development of the Child** Stuart S Stevenson associate in child health, Harvard Medical School and Harvard School of Public Health

5 15-6 00 **Influence of Endocrine Dysfunction on Acceleration or Retardation of Growth and Development in the Child and Adolescent** Nathan B Talbot assistant professor of pediatrics, Harvard Medical School

CORRESPONDENCE

PSYCHOSOMATIC MEDICINE

To the Editor I really enjoyed the excellent editorial on the meaning of psychosomatic medicine, which appeared in the January 9 issue of the *Journal*. In numerous places I have protested against the absurdities that the term "psychosomatic medicine" has somehow launched into clinical thinking. The effect of emotions, as organic events, on bodily structure is as old as Hippocrates, and long before Dunbar's book this was stressed in the literature by both experimental and clinical workers. Of course, all emotions are potent organic events, just as all experience changes bodily structure either transiently or permanently.

It is a far cry from this, however, to the fantastic ideas that the psychosomaticists have introduced into medicine. A misstep morally makes one slip on the ice twenty years later and break an ankle or the neck as a punishment self-inflicted by unconscious guilt. All kinds of nonstatistical and utterly unproved work asserts that this or that aggressive or non-aggressive trait is responsible for accidents, heart disease, ad lib, ad glib, and ad nauseum. The pediatricians, the orthopedic surgeons, the internists, indeed all kinds of physicians have taken it up so that, as one lady expressed it to me recently, it is rather dangerous to consult about a bodily disease at present, for you are accused of all kinds of things that have occurred in your childhood.

I plead guilty, for I have already introduced the word "somatopsychics" into the literature via two papers one of which was published with that name as part of the title. I agree that neither psychosomatics nor somatopsychics is a necessary word. I believe, however, that merely stating that

an experience, of whatever sort, creates bodily disorder is insufficient since the "experienter" is as important as the "experience." There are people with constitutions predisposed to fear, depression and disastrous somatic responses to experience. Whether the constitution is acquired early through conditioning or inheritance is important, but the treatment does not depend finally and fundamentally on psychologic grounds—it rests on reorganizing physiology. That there is a bodily basis to the mental diseases, whether they are organic or functional is, so far as I am concerned, the proper working hypothesis of psychiatry. Every emotional experience activates bodily changes, and even if mental disease can be traced to emotional experiences, the bodily changes would still have to be understood and accounted for to bring about cure.

Psychosomatics talks much but cures little. The real therapeutic triumphs in psychiatry, as yet imperfect, are physiologic—insulin coma, electric and metrazol shock, prefrontal lobotomy and the use of Dilantin and other drugs. There are few who can live with an emotionally placid mood in an extremely troubled world.

ABRAHAM MYERSON, M D

171 Bay State Road
Boston 15

DEPRIVATION OF LICENSE

To the Editor At a meeting of the Board of Registration in Medicine held January 16, it was voted to suspend the license to practice medicine of Dr Marguerite Krausz, 8 Winter Street, Boston, for three months because of gross misconduct in the practice of her profession.

H QUIMBY GALLUPE, M D, Secretary
Board of Registration in Medicine

State House
Boston

BOOK REVIEWS

Local Health Units for the Nation. A report. By Haven Emerson, M D. With the collaboration of Martha Lubinbuhl, M A. 4th paper, 333 pp., illustrated. New York: The Commonwealth Fund, 1945. \$1.25.

This book is the report of the Subcommittee on Local Health Units of the Committee on Administrative Practice of the American Public Health Association. It discusses the existing local public-health services in the various states and makes suggestions for improved service. The book is largely composed of tables showing existing personnel and annual budgets for local health services, together with similar tables for an improved service. Each state is discussed separately.

This volume should be of value to health administrators, physicians and lay persons interested in improving public health.

Public Medical Care Principles and problems. By Franz Goldman, M D. 8th, cloth, 226 pp. New York: Columbia University Press, 1945. \$2.75.

In this volume the author considers the problem of adequate medical care, describing the facilities that have been utilized in various countries in the past four centuries. The evolution of the public hospital, the transition from the primitive dispensary to the public medical center and the various methods employed in medical programs for persons in need are discussed.

In the last chapter the author outlines his solution of the problem as follows:

It appears, then, that there is only one single method that would avoid the disadvantages inherent in other approaches to the problem of organizing payment for facilities and services: public medical care for all, with every necessary service provided as a right and free of charge. Such a system exists in Russia.

Regardless of whether one agrees or disagrees with the author's plan for medical care, his presentation of the changing patterns of medical service makes this book worth reading, and the extensive bibliography enhances its value.

Mitchell-Nelson Textbook of Pediatrics Edited by Waldo E. Nelson, M.D. 4th, cloth, 1350 pp., with 519 illustrations, 26 in color. Fourth edition, revised. Philadelphia and London: W. B. Saunders Company, 1945. \$10.00.

This composite authoritative standard treatise, the work of forty-nine contributors, first published in 1933 and last revised in 1941, has been completely rewritten and to all intents and purposes is a new book. Some alteration has been made in the general arrangement, a number of new sections have been added, and some sections of the previous editions have been discarded. It has been the aim of the editor to provide a textbook for the undergraduate medical student, the pediatrician and the general practitioner. The text is printed in a two-column format, with a good type on heavy paper. The volume because of its weight is difficult to handle. It is suggested that future editions or printings be made with a lighter paper, especially because the illustrations do not require the heavy paper. The book is recommended for all medical reference collections and to physicians interested in pediatrics.

The Physician's Business: Practical and economic aspects of medicine. By George D. Wolf, M.D. With a foreword by Harold Rypins, M.D. Second edition. 8th, cloth, 433 pp., with 58 illustrations. Philadelphia: J. B. Lippincott Company, 1945. \$6.00.

Medicine is undoubtedly an altruistic profession in many ways, but the physician is entitled to a just compensation for his services. Dr. Wolf has analyzed medicine as a business and in this book has made his studies available to the medical profession. This second edition has been thoroughly revised wherever possible. New chapters on workmen's compensation laws and prepaid health insurance have been added, but the material on postgraduate study and war careers for physicians other than private practice have remained unaltered, because of the changing situation in these fields. The location of a practice, contacts with other physicians, specialization and the proper conduct of an office, including finance and insurance, are adequately discussed in a simple manner. There is an important chapter on the legal relations of the physician to his patients and the community. This book should prove of value to all physicians and should be in all medical and business libraries.

Hypnoanalysis. By Lewis R. Wolberg, M.D. With a foreword by A. Kardiner, M.D. 8th, cloth, 342 pp. New York: Grune and Stratton, 1945. \$4.00.

The first part of this book comprises a complete report of a hypnoanalysis in an individual case of schizophrenia, with a dynamic interpretation of the protocol, involving the use of hypnosis as a therapeutic agent and resulting in a return of the patient to normal. The second is devoted to an extended consideration of the theory and practice of hypnoanalysis, including the relation of psychoanalysis and hypnosis.

The Psychoanalytic Theory of Neurosis. By Otto Fenichel, M.D. 8th, cloth, 703 pp. New York: W. W. Norton & Company, Inc., 1945. \$7.50.

This book is in all respects an informative, systematized, reference text in psychoanalysis. The title is thus quite incomplete and perhaps misleading, not only the psychoanalytic theory of neurosis but also nearly all aspects of the psychoanalytic field in the frequently encountered psychogenic disorders are dealt with. Practically every phase—in fact almost every statement—is bibliographically covered and referentially indexed, so that there is no doubt left for the reader concerning where the weight of the opinion and experience of other workers and the author is directed.

A detailed description of the book would necessitate a repetition of the chapter headings. The development, description and therapeutic consideration of so-called "functional" emotional illnesses, however, are delivered so painstakingly and concisely that at times the reader may believe that Dr. Fenichel is giving him a personal series of lectures in these subjects. The abundantly illustrative case material does not tax the reader to find the desired examples.

Depending on the background of the reader, a certain amount of dissension may arise with the inclusion of manic depressive and schizophrenic syndromes and standard psycho-

pathic personality pictures (character disorders) in a psychoanalytic text. The descriptions of these conditions are not presented, but the pathogenesis of each major symptom is discussed according to psychoanalytic principles. The terms used in the following typical description may be somewhat distorted so as to reflect chiefly analytic principles: "The hypertrophy of the reassuring infantile partial instinct simultaneously serves as a safeguard to maintain the repression of the Oedipus complex and of other warded off remainders of infantile sexuality." A tilt with a wooden spear is made against "constitutional determinists" who employ Latin neologisms in the discussion of fixation.

Schizophrenia, as is frequently done, is dealt with as a repression, extending back, at least in part, to the narcissistic level. The important symptoms of schizophrenic psychoses are analyzed and, in a sense, genitalized. Hallucinations are considered capable of interpretation in the same way as dreams. Delusions are regarded as misjudgments of reality based on projection—representing an attempt to supplant the last parts of reality, they often contain elements of the repudiated reality and portions of warded off drives as well as projected demands of the superego. Paranoia and paranoid schizophrenia are believed to differ in that in the former "a more fortunate constellation of psychological forces permits a definite encapsulation of the pathological process."

Echolalia, echopraxia and automatic obedience are also attributed to primitive attempts at regaining contact. The infantile "mimetic expressions" are considered in apposition to simultaneous "warded-off hostile impulses" and "magic gestures" indicating "desired behavior of other persons in the future." Catatonic rigidity is held to reflect a conflict between the impulse to act and the defense against it. Borderline cases are discussed without—in the reviewer's opinion—the careful directiveness that characterizes the bulk of the text, issue may be taken with the following quotation:

potential schizophrenics have not broken with reality yet, though they show certain signs of beginning such a break and, under unfavorable circumstances of life, may develop into psychotics, or they are persons who have "channelized" their schizophrenic disposition, eccentrics who are crazy in one more or less circumscribed area and otherwise retain normal contact with reality. One might also question the terms "partial delusions," "partial hallucinations" and "partial stereotypes."

Aside from the perilous trip through the schizophrenic channel in which many workers have floundered, Dr. Fenichel's book is praiseworthy in all respects. The avoidance of numerous references to classic and popular dramatic literature is as refreshing as the use of well known English expressions and idioms. This is not an elementary text for popular reading but a real psychoanalytic reference book for the psychiatrist.

Men Without Guns. Text by DeWitt MacKenzie and descriptive captions by Major Clarence Worden, Medical Department, United States Army. With a foreword by Major General Norman T. Kirk, surgeon general of the United States Army. 8th, cloth, 152 pp., with 137 plates. Philadelphia: Blackston Company, 1945. \$5.00.

This book is based on the work of twelve distinguished artists who were assigned to theaters of action in Europe, the Pacific, the India, Burma and China front and hospitals at home and abroad, training centers and industrial plants in the United States. The artists did their sketches and paintings on the spot. Among the subjects dealt with are the training of physicians and enlisted corpsmen, the production of medical and surgical supplies, the movement of men and supplies in combat areas, the general hospitals, including surgery, convalescence, rehabilitation and occupational therapy, the Army Nurse, the hospital ship, aviation medicine and the performance of the Medical Corps in actual combat zones. Although the artists who went to the front were in actual combat zones and were exposed to diseases of all kinds, none were injured or became ill. The humorous side is not neglected, serving as a bold relief to the serious care of the wounded and ill.

Most of the reproductions are in color and are excellent. The descriptive text is well written in an easy, narrative style and covers the Southwest Pacific, Saipan, Italy, D-Day in Normandy and the Burma Road. This work is an out-

standing graphic contribution to the medical history of World War II and should be in all libraries, public and medical

Science and Scientists in the Netherlands Indies Edited by Pieter Honig, Ph D, and Frans Verdoorn, Ph D 4^o, cloth, 491 pp., with 134 illustrations New York Board for the Netherlands Indies, Surinam and Curaçao, 1945 \$4 00

This collective work, in which the science of the Netherlands Indies is discussed by a number of authorities in special fields, contains some material of medical interest. Five chapters are devoted to the history of the cultivation of cinchona. There are short chapters on veterinary service, beriberi, rabies, medical research, medical education and missionary physicians and hospitals. The larger part of the text is devoted to the natural sciences and chemistry. A valuable compilation of scientific institutions, societies and research workers in the Netherlands Indies will be found in a supplement. A few contributions are written in French and German.

The work is not well arranged from the point of view of subject relation. The text is printed in two columns, and the book is too heavy for its size owing to the weight of the coated paper not required for the kind of illustrations used in the text. The type is much too small for comfortable reading. A lighter paper and larger type, although increasing the number of pages, would have produced a lighter and much more satisfactory volume. The work is valuable, however, in providing a story of science in the Netherlands Indies.

Pathology in Surgery By N Chandler Foot, M D 4^o, cloth, 511 pp., with 368 illustrations and 10 plates Philadelphia J B Lippincott Company, 1945 \$10 00

Dr Foot has written a short book on his personal experiences as a surgical pathologist. Informality in a scientific text is unusual, but it makes the book more readable. It would be almost impossible to cover the entire field of surgical pathology in less than five hundred pages that include almost four hundred illustrations, but the author has tried to do this and in addition has considered many medical conditions in which biopsies are occasionally performed, with the result that he does not do justice to some of the more important surgical lesions. For example, there is no need to spend an entire page on chronic glomerulonephritis and nephrosclerosis. Anyone interested in this subject would naturally consult a textbook on general pathology.

The title implies an exposition on the pathology seen at the operating table. In fact, the fly leaf of the book states, "It is a thorough coverage of the close relationship between the pathologist and the surgeon in the operating room." Unfortunately, the book does not emphasize this aspect because it seriously neglects gross pathology, gross descriptions of pathologic lesions, by and large, being skipped over hurriedly. This might be excused if sufficient gross illustrations were used, but of the three hundred and sixty-eight illustrations, there are only four black-and-white photographs of gross specimens and six color plates, each containing only a few colored drawings of some of the most frequent pathologic lesions, such as appendicitis, cholecystitis and cancer and cysts of the breast.

The competent surgical pathologist is the one who is able to make a diagnosis grossly in the operating room. For example, the most frequent lesion for which the pathologist is called to the operating room is a lump in the breast. The author states, in relation to tumors of the breast, that the surgeon should "cut down upon the tumor and remove a generous biopsy (if not the entire growth)" rather "than to putter with aspiration biopsies." He continues "Should the freezing microtome produce sections that reveal cancer, the operation for radical mastectomy should then be undertaken without further delay, should a nonmalignant growth be diagnosed the wound is then closed up forthwith and the patient returned to her bed. Seldom if ever is it necessary to await the examination of permanent sections from paraffin blocks, although once in a great while a frozen section may give clinical evidence that requires further investigation." From this statement it appears that the pathologist should make frozen sections of all tumors of the breast. In the reviewer's experience most pathologists are able to make a gross diagnosis of lesions of the breast in about 90 per cent of

cases, and often when the gross diagnosis is in doubt the frozen section does not help.

The emphasis throughout this book is placed on the microscopic appearance of pathologic lesions, and many of the photomicrographs are excellent. Some are poor, however, and occasionally, as in the chapter on bone marrow, the text describes many cellular details without accompanying photomicrographs.

The chapters on lymph nodes, spleen and skin contain excellent photomicrographs, and the subjects are well presented. With the increase in chest surgery one would have liked to see a fuller presentation of bronchiectasis and the mediastinal tumors. The handling of the pathology of the adrenal tumors is superficial, in contrast to the fuller discussion of their endocrine aspects. The pathology of the uterus and cervix are considered together, and the fact that their clinical, surgical and pathological features are different is not brought out.

The text is well indexed, and a good list of recent references is given at the end of each chapter.

Personality Factors in Counseling By Charles A Curran, Ph D With a preface by Michael J Ready and an introduction by Carl R Rogers 8^o, cloth, 510 pp., with 71 illustrations New York Grune and Stratton, 1945 \$4 00

The introduction and the preface of this book call to the attention of the reader the need for better interpersonal relations and the dangers implicit in the limitations of individual freedom by various autocratic social systems. A tentative promise of changing emotional disturbance into an understanding, contented, maturely deliberative status is given in twenty counseling interviews.

The text, however, without any statement of principles, methods or technics launches into what is termed a typical, nondirective counseling procedure, the author taking it for granted that the reader is aware of the fundamentals. Automatically recorded interviews are then shown to be better than written or memorized interviews. Actually, several other texts on nondirective counseling are required as a preamble to an understanding of this one. About a hundred pages of the text are devoted to a statistical consideration of the responses or statements of one case. Positive statements, indicating improvement, and negative statements, indicating no progress or regression, have been counted by "judges" and arithmetically projected on increasingly complex charts, finally to be treated by chi-square formulations, which are intended to demonstrate that nondirective counseling brought about improvement in an emotional or anxiety-laden condition. The reviewer would like to believe that personality factors, insight into conflicts and certainly expressions of behavioral adjustments could be statistically evaluated. This wish is still unfulfilled after reading this text. One might similarly count the number of times a patient refers to himself in a number of interviews and mathematically derive an "egocentric ratio," which might then be employed in comparative personality studies. The statistical features in this book seemed to be similarly syllogistic.

In studying the content of the illustrative interviews one is impressed by the fact that "the therapist" (the author) merely echoes or paraphrases what "the client" has previously said—returning the expressions in words more meaningful to "the client" and understanding (by inference) the important affective alterations in the course of the therapy. If this is nondirective counseling, it should be as clearly stated as the suggestions or implicit assurances that improvement is noticeable. It is indeed distracting to note the avoidance of the terms "patient" and "illness" in the consideration of what, on the evidence presented, could very well have been neurotic anxiety and other emotional disorders. The lack of mention of any presenting psychosexual conflict would be amazing if the counseling were not maintained on a superficial level.

In spite of the foregoing the reviewer is cognizant of the author's unlimited patience and considerable knowledge of and rapport with the more important human emotional modalities. The author's counseling ability is known to be equaled by that of few people. It would have been more instructive for a man of his caliber to have written a book that abounded with much case material and a description of how nondirective counseling brought about a solution to presenting symptoms. Instead, this is a conglomeration of severely involved statistical formulations with their implications for future personality studies.

The reviewer believes that it is essential to delineate sharply the respective spheres of medical and nonmedical psychotherapeutic efforts. When can "a client" be classified as "a patient"? When does "a counselor" practice psychiatry without a license? Admittedly, even tritely, there is a lack of trained psychiatric personnel. This may not be the reason for the independent undertaking of rather extensive psychotherapy by nonmedical workers. That people take their troubles to anyone with a sympathetic ear has led to popularized concepts of counseling by such personages as Mr. Anthony and his imitators, the listening to troubles being thus made a financial enterprise. The dangers of such popular inclinations should be pointed out, standards planned and licenses issued accordingly.

With all the above in mind, this book can be of interest to statistically minded students of human emotions and behavior. To the average psychiatrist or to allied professional personnel, probably too much effort will be required in reading to make it useful.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Suggested School Health Policies. A charter for school health. Second edition. Revised by the National Committee on School Health Policies of the National Conference for Cooperation in Health Education. 8°, paper, 46 pp. New York and Minneapolis: Health Education Council, 1946. 25 cents.

This pamphlet, which is written as a guide for all concerned in school health, integrates the viewpoints of many professional groups on the contributions that school programs can make for the health of children and communities. The National Committee on School Health Policies consists of fifteen representatives of fifteen different educational, medical, social and public-health organizations. Eight of these organizations are medical in character, and the chairman of the committee is Dr. Charles C. Wilson. The program is an outline of six main divisions, as follows: provisions for healthful school living, health and safety instruction, services for health protection and improvement, health aspects of physical education, education and care of the handicapped, and qualifications of school-health personnel. There is a preliminary chapter on general health policies. The pamphlet includes suggestions for a school program. Appended to the text is a selective source bibliography on the various aspects of the subject. This pamphlet is recommended to all persons concerned with public health in the schools. It should also be in all public-health libraries.

A Malarialogist in Many Lands. By Marshall A. Barber, A.M., Ph.D. With a foreword by Paul F. Russell. 8°, cloth, 158 pp. Lawrence, Kansas: University of Kansas Press, 1946. \$2.50.

In this popular book Dr. Barber informally tells the story of his travels and experiences in the war against malaria. He has been chasing malaria plasmodia and their anopheline vectors for half a century in the United States, Central and South America, Europe and Asia. To Dr. Barber belongs the credit for discovering the effectiveness of Paris green as a larvicide. In conjunction with Justice B. Rice, he improved a cumbersome and laborious precipitin test so that it could be used rapidly and cheaply to determine the source of blood meals of thousands of mosquitoes. This basic work made it feasible to measure on a large scale the amount of contact between Anopheles and man, and thus to focus attention on the one or two species chiefly responsible for spreading malaria in any given region. In conclusion, Dr. Barber states that the amount of malarial illness rivals that of any other disease, except perhaps the common cold. He believes that all dwellings should be screened at night as a protection against the entrance of mosquitoes. A significant aspect of the book is the way in which it shows how the prevalence of malaria is related to environmental factors, such as flood, famine, irrigation and the presence of wild animals. The book is written in an informal, easy style and should find a place in all public and medical libraries.

NOTICES

ANNOUNCEMENTS

Dr. Archie A. Abrams calls attention to the omission of his office address and telephone number from the current telephone directory. His office is at 1093 Beacon Street, Brookline, and the telephone number is ASPinwall 8951.

Dr. Albert H. Covner announces the opening of his office, with practice limited to diseases of the heart, at the Hotel Breakers, 285 Lynn Shore Drive, Lynn.

Dr. W. Philip Giddings announces the opening of an office for the practice of general surgery at 266 Beacon Street, Boston.

Dr. Harry Portman announces his return from military service and the opening of his office for the practice of medicine at 769 Salem Street, Malden.

HOSPITAL RESEARCH COUNCIL

A meeting of the Hospital Research Council will be held in the Bigelow Amphitheater of the White Building, Massachusetts General Hospital, on Tuesday, February 25, at 4:30 p.m.

PROGRAM

Competition of Antitoxin and Lecithin for *Clostridium welchii* lecithinase. Drs. P. Zamecnik and F. Lipmann.

The Effect of Oral Streptomycin on the Intestinal Flora. Dr. L. W. Kane.

Disseminated Encephalomyelitis Experimentally Produced by the Use of Homologous Antigen. Dr. L. Raymond Morrison.

The Excretion of 11-oxy corticosteroid-like Substances by Normal and Abnormal Subjects. Drs. N. B. Talbot and F. Albright.

TUFTS MEDICAL ALUMNI ASSOCIATION

The annual medical alumni lecture will be presented at Tufts College Medical School on Wednesday, March 5, at 4:00 p.m. Dr. Curtiss B. Hickcox, professor and head of the Department of Anesthesiology, Temple University School of Medicine, will speak on the subject, "Development of Anesthesiology and Its Relation to Medicine in General."

AMERICAN CHEMICAL SOCIETY

A symposium "Antibiotics," with Dr. Chester S. Keefer serving as chairman, is included in the program of the coming meeting of the Northeastern Section of the American Chemical Society. This particular exercise will be held in Room 10-250, Massachusetts Institute of Technology, at 4:05 p.m. on Thursday, March 13. The first paper, "The Role of Antibiotics in Medicine," will be given by Dr. Keefer, the second, "Penicillin Chemistry and synthetic approaches," by John T. Sheehan of the Massachusetts Institute of Technology, and the third, "The Discovery and Development of Streptomycin," by Selman A. Waksman, of Rutgers University. A general discussion and questions will follow.

AMERICAN SOCIETY FOR THE STUDY OF STERILITY

The third annual convention of the American Society for the Study of Sterility will be held at the Hotel Strand, Atlantic City, New Jersey, on June 7 and 8, 1947. The general theme of the meetings will be that of attempting to disseminate to the physician treating marital infertility an overall picture of the latest advances in reproduction. The convention will include original papers, round-table discussions, scientific exhibits and demonstrations. Registration for the sessions is open to members of the medical and allied professions. Additional information may be obtained from the secretary, Dr. John O. Haman, 490 Post Street, San Francisco 2.

(Notices continued on page xix)

The New England Journal of Medicine

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Volume 236

FEBRUARY 27, 1947

Number 9

THE PHYSICIAN AND SCHOOL MEDICAL SERVICES

GEORGE M. WHEATLEY, M.D.*

NEW YORK CITY

THE participation of the United States in war brings, as an almost inevitable aftermath, a wave of popular interest in the health of the school child. After the Civil War, California passed legislation requiring the promotion of physical activities in all schools, and after World War I, many states enacted laws pertaining to medical examinations as well as to physical education. Today, stimulated by the Selective Service findings, a strong current of public interest has set in. No less than ten bills relating to school health were introduced in the Seventy-ninth Congress.

Considerable public money is now being spent on the school health program. Is it being spent wisely? The legislation referred to above demands even more expenditure. Health and education authorities charged with the responsibility for these programs need medical advice and guidance to develop effective programs. It is imperative that physicians give their attention to school health. Too frequently, policies have been made without the advice and co-operation of medical authorities.

With school health again on the threshold of further development, it is important to take stock of its assets and liabilities and to suggest ways in which organized medicine can further improve the health of school children.

PRESENT STATUS OF LEGISLATION

At present forty-three states have laws permitting or requiring physical examination of children in school. These laws should be studied in the light of modern knowledge about child health, because many should be modified or even repealed. Some of the statutes are too restrictive—for example, those specifying that no clothing or perhaps only the shirt may be removed, others are too specific—for example, those requiring a medical examination of every child every year by the school doctor and those requiring that the examination be done by one person, such as the teacher, principal or school nurse.

*Assistant vice-president, Metropolitan Life Insurance Company

Thirty-four states have mandatory statutes covering physical education, many of which also need study and modification, there is a great range in requirements, varying from ten minutes a day or one period a week to sixty minutes a day or five hours a week. In forty-five states health instruction is treated in more or less detail in the courses of study. Has a medical committee ever reviewed these questions to determine if up-to-date facts are being taught? In one state, at least, the medical society has appointed a committee for the purpose of reviewing the courses of study with the state education authorities.

The legislation has not been consistent at either the state or the local level so far as the governmental agency responsible for the health service is concerned. In thirty states with laws requiring physical examination, the education department has the responsibility in eleven, the health department in eight and the two jointly in the remainder. On the other hand, from prepared reports by state health departments throughout the country, it appears that in twenty-six states public-health agencies play some role in developing the health service at the state and local level. There is even greater confusion regarding jurisdiction on the local level. In urban centers with populations of 10,000 or more, education authorities usually control the health service, no data for rural areas and for communities with populations under 10,000 are available. Health departments, where they exist, render some service in these sections.

The data on the administration of school health service in urban communities are presented in Table 1. To complete the picture, the type of service rendered, the agency responsible and the amount being spent in rural areas must be known. More than half the school children in this country live in communities with populations of 2500 or less. The current nationwide study of child health services of the American Academy of Pediatrics¹ will no doubt supply information on this point. State and local medical societies however, can take steps to review

their local regulations to determine if it is necessary to repeal, modify or reinterpret any statute pertaining to school health with a view to improving the quality of medical services and bringing up-to-date health instruction to the schools

How much has been accomplished in the health of the child of school age? Since World War I, immunization against smallpox and diphtheria has become a standard practice by family physicians as well as by schools and public-health services. The science of nutrition has had widespread application

TABLE 1 Administration of School Health Service in Urban Communities *

RESPONSIBLE AGENT	COMMUNITIES WITH POPULATION OVER 100 000		COMMUNITIES WITH POPULATION OF 30 000-99 999		COMMUNITIES WITH POPULATION OF 10 000-29 999	
	NUMBER	PER-CENTAGE	NUMBER	PER-CENTAGE	NUMBER	PER-CENTAGE
Board of education	47	65	114	71	345	75
Health department	22	31	36	23	41	9
Joint	3	4	9	6	75	16

*Based on data contained in a study "Present Status of School Health Service and the Necessity for Health Department Participation," presented at a meeting of the Association of State and Territorial Health Officers, Washington, D C, April 12 1945

to these children. The legislation relating to medical inspections in schools has undoubtedly placed many children in the hands of physicians for treatment that otherwise might not have been received. Health education through physicians and nurses and through other channels, including the schools, has brought knowledge about available health protection to many homes. The application of this knowledge is reflected in the spectacular decrease in mortality rate among children five to nineteen years of age (Table 2). The decrease in the total death rate was 64 per cent in the group five to nine years of age, 59 per cent for children ten to fourteen years of age

TABLE 2 Death Rates from All Causes among School Children *

AGE GROUP	DEATH RATE		DECREASE
	1923	1943	
	per 100 000	per 100 000	%
5 to 9	250.9	89.8	64.2
10 to 14	194.9	79.5	59.2
15 to 19	350.2	157.9	54.9

*Based on data available from Metropolitan Life Insurance Company

and 55 per cent for those fifteen to nineteen years of age. Tables 3 and 4 demonstrate the decline in some of the principal causes of death. Automobile accidents in the group fifteen to nineteen years of age, as might be expected, constituted the only cause that registered a percentage increase.

These accomplishments are the result, in part at least, of better child care administered by family physicians and parents, but school nurses and physicians and teachers have made some contribution,

although an immeasurable one, through their teaching and alertness to the signs of illness and through periodic medical inspection. In spite of this undeniable improvement, certain aspects of school

TABLE 3 Death Rates from Specified Causes among School Children Five to Fourteen Years of Age *

CAUSE OF DEATH	DEATH RATE		DECREASE
	1923	1943	
	per 100 000	per 100 000	%
Communicable diseases† (including diphtheria, scarlet fever, measles and whooping cough)	41.3	3.1	92.5
Tuberculosis	21.1	4.3	79.6
Pneumonia†	18.0	4.4	75.6
Rheumatic fever and organic heart disease	20.7	8.0	61.4
Appendicitis	13.6	4.0	70.6
Accidents total	45.5	25.6	43.7
Accidents, automobile	18.3	8.8	51.9

*Based on data available from Metropolitan Life Insurance Company

†Comparison of 1922-1923 with 1942-1943

health service should be strengthened if the advance in child health is to continue.

In localities where such services exist, there is frequently inadequate quality of medical service in the school, and relations with the practicing physicians and other treatment resources in the community are poor. There has also been lack of co-operation between the education and public-health agencies in the community, and the health services in the school have not been planned to provide a satisfactory learning experience for the children.

The following points are essential to the improvement of school medical service: co-operation between education and public-health authorities, provision for health services in the school that are satisfactory learning experiences for children, properly qualified school health personnel and the development and strengthening of relations with the medical profession. Obviously, these four factors do not com-

TABLE 4 Death Rates from Specific Causes among School Children Fifteen to Nineteen Years of Age *

CAUSE OF DEATH	DEATH RATE		DECREASE
	1923	1943	
	per 100 000	per 100 000	%
Tuberculosis	110.7	23.8	78.5
Pneumonia†	45.4	10.0	78.0
Appendicitis	15.4	4.7	69.48
Rheumatic fever and organic heart disease	28.9	14.3	50.5
Accidents total†	55.5	38.1	31.4
Accidents, automobile†	11.1	18.1	63.1 (increase)

*Based on data available from Metropolitan Life Insurance Company

†Comparison of 1922-1923 with 1942-1943

‡Comparison of 1923 with 1941

prise all the elements of the school health program. For a comprehensive outline of policies relating to the entire matter, the Committee on School Health Policies of the National Conference for Co-opera-

tion in Health Education² has recently published recommendations that every physician should read

CO-OPERATION BETWEEN EDUCATION AND PUBLIC HEALTH

Too often, educational and health authorities have been at odds over the responsibility for running the program of school health. Health departments in nearly every state are involved, but so are education departments. Whatever service is rendered by health departments to children while they are in school involves the school administration. The schools include about one fifth of the total community population, and everyone has had contact with the schools. It is the only agency employing trained educators in the ratio of 1:40 in the population reached. Moreover, it is another avenue to the home. On the other hand, the public-health department knows the health problems, the health facts and the health resources of the community.

A growing number of health officers and school administrators are discovering the help that they can be to each other. In some places the two departments, with the aid of other interested groups such as the medical society, have developed a statement of policy to cover school health work. The recommendations of the Committee on School Health Policies,³ referred to above, were an outgrowth of a state committee that the Connecticut State Medical Society helped to initiate. Some states have made formal arrangements to continue this co-operation by establishing a joint committee or council of state and school health. A recent inquiry sent to health and education departments in the United States revealed that practically all the states have some machinery for co-operation between the two departments and that twenty-seven have formal plans for such co-operation. The war appears to have been a factor in stimulating closer working relations between the departments — just as it has between nations. Such a union cannot be dispensed with, any more than that of the nations can.

MAKING MEDICAL SERVICE A LEARNING EXPERIENCE

The two prime purposes of school-health services are to reveal health problems and thereby to call the child to the attention of his physician for treatment, and to create in the child and the parents understanding and desire for preventive medical service.

Medical examination in schools — as performed annually or routinely — has been severely criticized both as a costly and inaccurate case-finding method and as an unfortunate educational experience. Since educators and pediatricians realize that medical procedures in schools have educational implications, the trend is toward fewer but more thorough medical examinations for individual pupils. The value of

the presence of the parent at the examination, especially of younger children, in terms of health education as well as treatment, has been demonstrated, 25 per cent more children received medical care when the parent was present than when the parent was absent. The school physician, in appraising the health status of the child, should utilize information based not only on the physical examination but also on the interview with the parent and, frequently, with the school nurse, teachers and other members of the school staff. The school examination should include a conference with the parent of the young child and with the older child himself, to review the findings, to plan care, to give personal health guidance and to interpret the child's health needs.

That this goal has not been attained may be surmised from the comments of high-school students on their medical examinations in the school. "The whole impression you get," said one boy, "is that it [the medical examination] is something that applies to gym and that all they want to do [meaning the school authorities and physicians] is be sure that you can stand up long enough to get through it." Another student remarked "There are questions we should like to ask the doctor, but he is always in such a hurry." "The school doctors don't examine you all over," another youngster complained, "they take a look at your eyes and, if you happen to have a sore throat, they tell you to get your tonsils out." Other children stated that the schools should provide doctors who are interested and doctors who like their profession. Obviously, these students found the medical examination a superficial, hasty procedure conducted by a physician who did not ask questions about health, in spite of the fact that the medical profession has long maintained that the school medical examination is the most "teachable moment" — the best educational opportunity that exists in the schools.

PREPARATION OF PERSONNEL

The medical examination of school children is usually performed by a part-time physician — a local practitioner, as a rule — who is poorly paid for this work and who is usually given no opportunity for special preparation for it. If the average school physician has received instruction regarding his task, it usually concerns fulfilling the letter of the law. When the law requires annual, biannual or routine examinations, the physicians are put under pressure to do them as rapidly as possible. This results in fifteen, twenty or even sixty examinations an hour, with the result that the medical findings are often valueless. For example, the recent study of findings among the Massachusetts high-school students in 1941, as reported by Southworth, Laumer and Turner⁴ shows a tremendous difference in the defects found among pupils in various schools. Postural defects range from 1 to 80 per cent, dental ab-

normalities from 5 to 79 per cent, visual deficiencies from 0.9 to 36 per cent and cardiac anomalies from 0.3 to 9 per cent. Whereas some difference between schools and communities is to be expected, the variation is so great as to place the validity of the findings in doubt. Physicians have a responsibility to help to improve the quality of health examinations in schools.

Education of the School Physician

An extremely significant development regarding improvement in school health examinations is the publication by the American Public Health Association of a statement on the training and qualifications of school physicians. This report emphasizes the value of experience and instruction in pediatrics and education. The position of a school physician requires specialized public-health training, as well as a knowledge of the characteristics and behavior of normal and diseased children.

At the University of Michigan, a scholarship was recently established whereby a physician serves as assistant resident and resident in the Department of Pediatrics for twenty-four months. He also takes courses in the School of Public Health, after which he serves for at least a year as a full-time school physician at an annual salary of \$6000. It is hoped that this may influence some physicians to enter the field of school health administration as a career.

The bulk of the preparation of school physicians is of necessity on-the-job training. In some communities time is set aside for meetings where the physicians are given instructions in certain aspects of child health and may even be given some understanding of modern education. Physicians welcome the opportunity to learn about school health when they obtain this knowledge from competent authority. State health departments, in co-operation with education departments and the medical societies, can and should help. Regional conferences or institutes can be held, authorities from medical schools, teacher-training institutions and schools of public health being invited to participate.

The administration and continued development of health services along the lines proposed require supervisory personnel. Physicians doing school work need the leadership and guidance that competent medical supervision can give. In most states, except for a few urban communities, this supervision is woefully deficient.

Consultant Service

Some school health programs have developed consultant service for special health problems revealed by the examination. For example, heart disease, which is a relatively frequent and serious finding in children of school age, is difficult to diagnose. Some communities do not permit the removal of clothing, the physician does not have the advantage of fluoro-

scopic or x-ray equipment or other laboratory aids essential to the diagnosis. In New York City, Cincinnati, Rochester and Syracuse, school children are referred by school physicians to a specialist, who has the advantage of more time and laboratory aids for a diagnosis. This service, which is provided with the approval of the medical society, is similar to that provided by health departments for the diagnosis of tuberculosis and some other diseases. By this careful procedure, more accurate diagnosis for a serious condition is assured, and modification of the school program can be based on a clearer understanding of the child's potentialities.

Medical Advisory Functions

Instead of giving all his attention to finding defects, the school physician should be encouraged to develop the guidance aspects of his services. His value to a school should be measured in terms of the advice he gives to the children, parents and teachers with whom he comes in contact. He should assume professional leadership, establishing relations with private physicians and clinics and bringing all community resources into closer connection with the school.

He should help to keep teachers conscious of health. When teachers have been properly informed what to look for in the behavior and appearance of pupils and encouraged to refer children to the physician, 80 per cent of the children will be found to merit his professional services. His work should be co-ordinated with that of the nurse at the time of the examination so that undivided attention is given to each child and parent. He should concentrate his efforts in the examination on the discovery of poor health habits, gaps in the knowledge of parents about health matters, health problems suspected by teachers, defects that obviously hamper learning and medically neglected children. These problems exist at every grade level. The program should be flexible and permit the school physician to be of service to children at any time in any grade.

With the parent present at the examination, with stress on adequate history taking, with emphasis on the interpretation of his findings to parent, nurse and teacher and with careful attention to the planning of aftercare of the child, the school physician can meet his educational opportunities and responsibilities. Under these conditions, his data are adequate, for he has not neglected facts provided by the teacher and the parents that relate to the educational, emotional and social problems of the child. His attitude toward his work will be more confident because he has a clearer understanding of his function in relation to the school and the community. His professional morale will be strengthened because he is giving his best judgment in a variety of ways each day.

THE TEACHER'S ROLE IN HEALTH SERVICE

Nyswander⁴ demonstrated that the teacher's responsibility for observing the health of pupils can be made an effective part of the school health service. Teachers were prepared to observe and report to school nurses the health condition of pupils. The annual medical inspection was replaced by annual and semiannual conferences between the classroom teacher and the school nurse. After teachers had received preparation, eight out of every ten children selected in these conferences, when examined subsequently by the school physician, were found to have a health condition requiring further medical attention. The study also revealed that teachers need more knowledge of and experience in observing health behavior and recognizing health deviations. It should be understood that this preparation of teachers is not for the purpose of assuming work to save the time of nurses and physicians, but primarily to enable the teacher to perform more adequately an important responsibility. The Michigan Superintendent of Schools⁵ has published a helpful guide to aid teachers in the observation of the health of pupils.

In reply to a recent inquiry that I forwarded to state education and health departments regarding teacher participation and observation of the status of the health of pupils, twenty-three out of thirty-six states recognized the value of teacher observation and the need for material, and eleven states had already prepared such material.⁶

MEDICAL RELATIONS

The most important aspect of school health service is that of the medical relation between the school medical service and the facilities for treatment in the community. As pointed out above, the main objective underlying the school health service is to ensure that something is done about children who have adverse health conditions.

With the development of school health work in this country, the case-finding or examination program has been considered the responsibility of the school physician, and treatment that of the community physician. The community physician may work in a clinic or in his own office, the family or community may pay him a fee or the service may be covered by some type of prepayment plan. Regardless of the circumstances governing the method of distributing medical care, what is done for the child depends on the knowledge, interest and skill of the physician, as well as the available resources for diagnosis and treatment. There is a gap between the physician who finds a problem and the physician who solves the problem, the road from the school to the source of treatment has been called the pathway to correction. Efforts to bridge that gap have occupied many millions of hours of

thousands of faithful, earnest nurses, many of whom were guided by little or no direction or information. Frequently, the family never had any clear concept of its responsibility. And when the gap seemed bridged and the child was taken to a physician for further examination, the school's diagnosis was wrong or rejected, or no treatment or improper or inadequate treatment was given.

The school can be of aid in improving medical relations by developing in those who provide the treatment understanding and co-operation regarding the case-finding work in the schools. Many practitioners are indifferent to or perhaps hostile to its aims. I have known such physicians who regarded the school health service as meddling with their patients. I have observed that mutual interest in the health of the child is usually a common ground for understanding. When the practitioner understands that health service can aid him both in diagnosis and in follow-up study, as well as treatment in special circumstances, he becomes the essential link in the chain of health care for the child. Practitioners in the community need to be kept informed of school health practices through their meetings, bulletins and so forth.

The school must also create confidence on the part of the practitioner in the school's medical findings, which the physician often mistrusts. He has had children referred by the school for treatment when he has already advised the family, on the basis of previous knowledge and observation of the child, that such treatment was not necessary. In individual cases, the remedy lies in informing the practitioner of the circumstances behind the referral. For example, in a case of diseased tonsils, the family physicians may not have seen the child for a year or more, although the child may have been sent home by the school nurse with acute tonsillitis on more than one occasion during this period. If the school puts this information in the referral note to the practitioner, his diagnosis and treatment may be influenced.

Pediatric and other consultative services should be provided for the physician. Many of the conditions in school children requiring treatment call for special professional skill — for example, dental care, visual and hearing defects, and rheumatic fever and rheumatic heart disease. This is particularly true in rural areas, where specialists in these fields are often not available. The element of higher costs is also involved in the treatment of these conditions.

The development of methods based on these principles would improve medical relations with the physician, in both the office and the clinic, concerning what goes on in the school, how the school health service functions and what the health needs of children are and, most important, would encourage the use of all the modern facilities for diagnosis and treatment. The attainment of this

end calls for special training of school physicians and nurses to aid them in their work with individual physicians in the community

Another principle, which is a logical development at this point, is the greater participation of the community physician in case-finding and in the medical examination. The gap between finding the case and obtaining treatment was mentioned above, and some ways of bridging it have been suggested. Another means is to have the school examination done by the community physician. Many school systems have rejected this idea—some on the grounds that if the outside physician is encouraged to participate, the school physician will not have a job, and others on the basis that examination by the former is not so carefully done as that done by the latter. But many children have had some medical attention prior to entering school. Therefore, the family should be encouraged to employ the physician to whom the child may already be accustomed and who, under these circumstances, may know far more about the child's health than the school physician is likely to learn from the brief contact with the child in school. If treatment is needed, the child is already at the treatment agency, and time would be saved in follow-up examination. Furthermore, if the physician carries a part of the responsibility for examination, the school physician will be released for further advisory service to principals and teachers in the schools.

* * *

Medical understanding and leadership are needed in the school health program. This is recognized by some state medical societies, one of which has encouraged county medical societies to name committees on school health, with the result that committees have been formed in forty-four out of sixty-one counties within the last two years. Recently, the Massachusetts Medical Society named a committee to study the ways and means of improving the school medical services.

Although school health has advanced from the earlier days when it was mainly concerned with the control of contagious diseases, there is a great deal of room for improvement. State laws are in many

respects outmoded. The quality of the medical service in the schools is often of a low order. Co-operation between health and education departments should be encouraged, and there should be a much closer working relation between the school and the practicing physicians in the community. A committee of a medical society might initiate specific activities to improve the quality of the school medical service. A program of teaching sessions, institutes or seminars should be planned in co-operation with health and education departments to refresh school physicians about child growth and development and other medical problems of children—especially nose and throat conditions, allergy, endocrinology, rheumatic fever and mental health. Standards of qualifications for school medical personnel should be developed and employed. A statement on the type of medical examinations to be done in the schools should be drawn up. If necessary, repeal, modification or reinterpretation of state laws to permit proper medical examinations in the schools should be obtained. Finally, adequate remuneration for the services of the school physician should be guaranteed.

The improvement of all service for children cannot take place without thorough understanding of current programs. If the health of children is to be safeguarded and necessary treatment given, planning of programs must be done in co-operation with educational and medical authorities in the community. Mistakes in school health programs are thereby less likely to be repeated, and some may even be rectified. Certainly, in this way, adequate health care and supervision of school children is likely to be achieved.

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REFERENCES

- 1 Editorial. EMIC program and child health in postwar world. *J Pediatr* 25:639-642, 1944
- 2 Health Education Council. *Suggested School Health Policies. A charter for school health*. Second edition. 46 pp. New York, 1945
- 3 Southworth, W. H., Laumer, J. V. and Turner, C. E. Study of health practices, knowledge, attitudes and interests of senior high school pupils. *Research Quart* 15 No 2 May 1944
- 4 Nyawander, D. *Solving School Health Problems. The Astoria demonstration study sponsored by the Department of Health and the Board of Education of New York City*. 377 pp. New York: Commonwealth Fund, 1942
- 5 *Teacher Observation of Health Conditions of School Children*. Published under the supervision of Eugene B. Elliott and H. A. Moyer. Bulletin No 325. 31 pp. Lansing: Michigan, 1945

PHYSICAL REHABILITATION OF DISABLED PERSONS*

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THE following statement of the purposes of rehabilitation programs¹ provides an excellent analysis of the co-operation of all groups that will be necessary

The goal of any rehabilitation program is to achieve the maximum function and adjustment of the individual and to prepare him physically, mentally, socially and vocationally for the fullest possible life compatible with his abilities and disabilities

In the establishment of any rehabilitation project it must be realized that industry is the keystone in the whole structure because industry must take the finished product and, by careful and selective placement, utilize these individuals within their capabilities. Labor must understand that the third phase of medical care — rehabilitation — is a service and right that must be made available to all citizens in a democracy and that they have a right to expect such opportunities. The medical profession, governmental and social agencies, insurance companies, and individuals must be made cognizant of the opportunities available in a comprehensive, well-rounded program of rehabilitation and that with such a program, handicapped individuals may be transformed from dependent invalids into contributing, self-respecting, self-supporting citizens.

Every social minded person will agree with these conclusions, and one of the greatest problems that the Nation faces today is the rehabilitation of the physically, emotionally and economically disabled. Eugene J. Taylor,² formerly chief, Education Branch, Convalescent Service Division, Office of the Air Surgeon, has summarized the implications of the question as follows

We had in America prior to the onset of World War II some twenty-three million persons disabled in some degree from disease, accident or earlier wars. Each year there are some 350,000 persons disabled outside of military service. We had in 1940 some six and a half million disabled males between the ages of 15 and 64 years, men who normally would be income-producing. These six and a half million plus the number of disabled or handicapped veterans being discharged from our military hospitals will give us, when demobilization is completed, approximately eight million working-age males who are disabled to the extent of requiring physical or vocational rehabilitation or special placement aids if they are to be adequately employed. This represents one person in sixteen in our general population and one in seven in our male working population.

We have had during four years of war, a total of approximately seventeen thousand amputations in the Army, but we have nearly 120 thousand amputations from disease and accident among our civilian population in that same period. Eleven thousand soldiers were wounded on the beaches of Normandy in the first ten days after "D" Day, yet even with curtailed traffic, automobile accidents alone accounted for more than twice that many civilian casualties in the same ten days.

The problem of the disabled and handicapped is not a new one. War has only focused the microscope of public interest on this great national problem and quickened the necessity for its solution.

The work of the Office of Vocational Rehabilitation has demonstrated how adequate vocational rehabilitation pays

off economically. The 43,997 persons undergoing vocational rehabilitation in 1944 received prior to their rehabilitation an average annual wage of \$148.00. After rehabilitation, the average annual wage of the group jumped to \$1768.00. For the entire group, prior to rehabilitation, the total earnings were \$6,510,556. After rehabilitation the earning power of the same group jumped to \$77,786,696. This gain represents a return of \$47 for every \$1.00 invested.

No amount of money can measure the social and moral satisfaction gained by the successfully rehabilitated and employed handicapped worker and his family. Nor can it measure the value to society of the transformation of these individuals from dependents to productive, self-reliant persons.

A study of the medical aspects of the problem indicates that the medical profession has often failed to contribute its share in attaining the objectives of rehabilitation. Physicians and surgeons have become so interested in the technologic phase of medicine that the humanistic aspect has often been forgotten, they have been so engrossed in treating the disease that the patient has often been forgotten. As a result there is a gap between the present practice of medicine and the needs of the patient. Unless the disabled person is rehabilitated to the fullest possible life compatible with capability, the physician has failed in his duty to the patient.

What are the basic needs of the disabled? In twenty-seven years of experience at the Institute for the Crippled and Disabled, such needs have been found to be the ability to walk and travel, to care for the daily needs and to have the maximum use of the hands. No patient should be discharged from a hospital until he has reached his maximum ability in attaining these three objectives.

The present procedures in a great majority of hospitals deserve consideration. The surgeon amputates the limb. The patient recovers from the operation in good condition, and the stump is all that could be desired. The surgeon is too busy from morning to night in consultation, teaching and operating to be expected to give the time to or become interested in the slow, laborious and protracted third phase of medicine. But someone must apply the bandages to shrink the stump, exercise what remains of the limb, prevent contractures, teach the patient how to use crutches and recommend the proper type of prosthesis. Many months later, the patient must be taught how to use his artificial limb in walking, climbing stairs, sitting down and arising from chairs, getting into or out of a bus or car and all the other activities necessary for daily living and working.

A prominent surgeon had a cerebral hemorrhage that resulted in a right hemiplegia. He asked his medical and surgical friends for assistance, and they all told him he had hemiplegia following a cerebral

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 23, 1946.

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hemorrhage "I know that," he said, "but what can you do to help me?" His desire was to learn how to walk, to care for his daily needs and to have the maximum use of his hands so that he could return to his practice of medicine. The morale of these patients quickly rises when they are taught to walk with a crutch or cane, to lace their shoes and tie a bow with one hand, to cut their own meat with a special knife, and to learn left-handed writing and the many other activities necessary for self-care.

Massage, electricity and exercise are useful forms of treatment, but functional activities to meet the needs of the patient have more basic therapeutic value because they lead to independence. Better results are obtained by working *with* the patient than by working *on* him.

More than a thousand soldiers, and many times that number of civilians, have a loss of motion and sensation of the lower extremities with incontinence, as a result of spinal-cord lesions. By proper rehabilitation procedures every one of these patients with a dorsal or lumbar lesion can learn to travel with braces and crutches and to care for his daily needs and can be trained in a useful vocation.³

The procedures for meeting the needs of the patient are a function of specialists in physical medicine. A recognition of the needs of the patient and the sources from which they may obtain help will aid physicians and surgeons to restore their patients to the maximum capacity.

The six principal groups of seriously disabled patients needing rehabilitation are the blind and partially seeing, the deaf and hard of hearing, the cardiac, the tuberculous, the neuropsychotic and those generally classified as orthopedic. The restoration of the person with a so-called "one-organ" or "special-organ" disability is not such a difficult problem, because only one organ is involved. The blind cannot see, the deaf cannot hear and the cardiac and tuberculous patients need guidance on the amount of work they can perform. Rehabilitation is infinitely complex in the neurotic and psychotic patients because of the influence of the mind on the body and the intangible intricacies thereof. Not much less difficult, however, is the rehabilitation of the orthopedically disabled because of the great variety of conditions that may occur. When one considers the hundreds of muscles, bones, ligaments and joints and the vast network of blood vessels and nerves supplying the extremities, the number of possible disabilities is impressive.

* * *

Rehabilitation begins on the day when definitive medical treatment is no longer required. The procedures that have been found most successful in Bellevue Hospital are as follows.

Consultation

When the physician or surgeon decides that medical or surgical treatment is no longer needed, the

physician in charge of physical medicine is called in consultation. No patient is accepted for treatment without a consultation. On the department referral form are recorded the patient's name, age, sex and vocation, the date of onset of the condition and the date of admission to the hospital. The intern or resident gives all the information concerning the patient and the re-establishment of function that is indicated. From this information the etiology, diagnosis and results desired are recorded.

If the patient is referred from the outpatient department, the information is obtained from the hospital records and the physician's referral form.

Physical Examination

The purpose of the physical examination is to obtain data concerning the disability resulting from the injury or disease, the extent of the disability and the handicap produced by the disability.

The disability The so-called "orthopedic disabilities" caused by congenital defects, disease or trauma affect the proper functioning of bones, muscles, joints, ligaments, brain and nervous system and produce disabilities limiting movement of the joints or action of the muscles. Fractures, tuberculosis and osteomyelitis of bones, arthritis of the joints, the dystrophies of muscle, sprains and dislocations produced by injuries to ligaments, cerebral palsy, brain trauma, poliomyelitis, multiple sclerosis and transverse myelitis that affect the brain and spinal cord produce disabilities that result in decreased motion or loss of motion at the joints or changes in the normal strength of muscles, or both. It is the physician's responsibility to record the disability, since rehabilitation is concerned with the incapacity and not with the diagnosis.

Extent of disability It is impossible to evaluate the results of treatment unless the extent of disability is recorded. This information is obtained for the physician by physical therapists who are trained in these procedures. The method of measuring and recording limitations of motion can be illustrated by the following case. A patient fractured the radius by falling on the ice. The fracture had healed, and rehabilitation procedures were indicated because of a flexion deformity at the elbow. The record of the physician disclosed that the cause was trauma, the diagnosis, a fracture of the radius and the disability, limitation of motion at the elbow joint. The extent of the limitation of motion had to be ascertained. The normal range of motion at the elbow is from 180° in extension to 35° in flexion. The therapist measured the range of motion with the goniometer and recorded the extent of disability as 140° in extension and 60° in flexion. This indicated that the patient needed 40° more motion in extension and 25° in flexion.

By this method of recording the limitation of motion, the physician can determine at a glance the extent of the disability. It is also possible to evaluate

the results of treatment by having the therapist remeasure the motion in the joint and record the findings on the chart each week.

When the disability produces muscular weakness it is necessary to evaluate the extent of disability by testing the muscular power of the parts of the body affected. The therapists have been trained to evaluate muscle power and the findings are recorded in the following manner. A patient with a "dropped foot" following poliomyelitis has a disability consisting of flaccid paralysis of the leg and foot, the extent of the disability being a trace of dorsal flexion, normal plantar flexion, poor inversion and good eversion. It is only when the strength of a given group of muscles producing a movement is known that the danger of overworking weak muscle groups may be prevented, the proper remedial exercises prescribed and the treatment evaluated. Muscle strength can be further evaluated by giving each of the twelve degrees of muscle strength a unit value of one — these are referred to as "units of motor function."

The handicap produced by the disability The purpose of any treatment is to prepare the patient to meet the physical demands of daily living and working. It is impossible to determine from the measurements of joint motion and strength the ability of a person to perform functional activities. The only method of evaluating such ability is to have the patient perform the activity.

What are the activities necessary for daily living? They have been found to be walking and traveling, caring for daily needs and the maximum use of the hands.

Our test of the physical demands of daily living consists of thirty-seven activities.⁴ The patient travels around the testing area performing each activity as he progresses. He is given instruction on the activity to be tried and the need for the activity in daily living. The activities that cannot be performed are included in the daily program.

* * *

The carrying out of such a program is part of the hospital treatment of every patient. Patients leaving the hospital should be able to walk and travel and care for their daily needs if the gap that exists between the practice of medicine and the needs of the patient is to be bridged. Physicians and surgeons do not have the time or interest to perform this evaluation and rehabilitation program, which should be carried out by specialists in physical medicine. The object cannot be accomplished by heat, light, water, massage or electricity or by weaving and making toys in occupational-therapy shops; it can be attained only by working with patients, showing them their limitations and motivating them to accomplish the activities necessary for daily living.

Before returning to work, a person who has been injured should be tested in the factors necessary for working. After seven years of research the War Manpower Commission⁵ published a book that gives an analysis of physical demands for several thousand vocations in terms of functional activities, such as walking, standing, pushing and lifting. Of the twenty-five activities listed, twenty depend on the movements of the joints and strength of the muscles. Before a disabled person is placed on a job the physician decides which of these physical factors he has partial capacity or no capacity to perform. It is my firm conviction, based on the experience gained from examining thousands of orthopedically disabled persons, that an attempt to predict the physical activities that can be performed by a disabled person on the basis of inspection or even of a muscle test is unscientific and unfair to the patient. No one can predict with any degree of reliability the compensatory ability of a disabled person to perform functional activities until he tests the person in that activity.

We are now developing a test that will indicate the ability to perform these twenty-five activities that the patient can take to his employer when he returns to work. The employer will thus be able to compare the activities essential to the job with the worker's ability to perform them.

* * *

In summary, rehabilitation of the physically disabled requires that definite procedures be followed to attain success. They are a knowledge of the cause, diagnosis and disability, an evaluation of the extent of disability in terms of limitation of motion and strength, an evaluation of what activities, essential to daily living and working, the disabled person can accomplish, and a program that teaches the patient how to achieve the maximum function for the fullest life compatible with his abilities and disabilities.

The accomplishment of these objectives is the function of physical medicine. They cannot all be accomplished in the hospital. In the near future every city will have rehabilitation centers, where patients will be sent after discharge from the hospital, in which the patients will live if they are ambulatory or to which they will report daily as outpatients if they can walk and travel. They will be required to work all day to attain their maximum physical, mental, social and vocational rehabilitation and adjustment. Such centers will enable a disabled person to retain his self-respect and become self-supporting. Industrial firms will save pensions. Labor will save a valuable workman. The Government will have another taxpayer. Relief rolls will be reduced. Thus, the third phase of medical care will be developed, and the gap that

exists between the practice of medicine and the needs of the patient will be bridged

REFERENCES

- 1 Sub-Committee on Civilian Rehabilitation Baruch Committee on War and Postwar Physical Rehabilitation and Reconditioning, June 26, 1945 Report. (To be published)
- 2 Taylor, E J Teaching about America's handicapped *Civic Leader* 13 (No 11) 1-3, 1945

- 3 Medical Rehabilitation Division United States Veterans Administration *What's My Score?* (Handbook for patients with disability resulting from spinal-cord injuries) 36 pp Washington, 1946 Government Printing Office, 1946
- 4 Deaver, G C, and Brown, M E *Physical Demands of Daily An objective scale for rating the orthopedically exceptional* 36 New York Institute for Crippled and Disabled, Studies in Rehabilitation No 1, 1945.
- 5 United States Emergency Management Office, War Manpower Commission *Physical Demands Analysis and Physical Capacity appraisal* 37 pp Washington D C Government Printing Office, 1946

A COMPARATIVE STUDY OF PENICILLINS X AND G AND CRYSTALLINE PENICILLIN G*

GEORGINE ROTMAN-KAVKA, M D,† HAROLD L HIRSH, M D,‡ AND HARRY F DOWLING, M D§

WASHINGTON, D C

FOUR different fractions obtained from the mold *Penicillium notatum* have been identified. These have been named penicilins F, G, K and X.¹ The two that have received the greatest attention are the G and X fractions. Many commercial preparations containing varying percentages of these two fractions have been employed clinically with little attention to the actual composition of each product. This practice seems to be justified if studies of these two fractions reveal no significant differences in their properties, but is not justified if either is found to be superior. Accordingly, a study comparing the absorption, excretion, therapeutic activity and toxicity of penicillin G and penicillin X, and the in vitro sensitivity of various bacteria to these fractions was undertaken. For this purpose, the following preparations were employed: commercial penicillin, which contained at least 90 per cent of penicillin G, crystalline penicillin G|| and penicillin X,|| consisting of 75 to 95 per cent of the active substance. Since there were no differences in the results obtained with the various penicillin X preparations, they are all referred to below as penicillin X. Commercial penicillin has been interchangeably called plain, regular, and ordinary penicillin and penicillin G.

Absorption and Excretion

Figures 1, 2 and 3 demonstrate the median values of the blood concentrations obtained at various time intervals with each preparation. The number of assays from which each of these values was determined varied between three and twenty-one. The blood concentrations obtained following the ad-

ministration of penicillin X were consistently higher, and the duration of bactericidal activity was longer, in comparison with those of commercial penicillin and crystalline penicillin G. No significant differences were observed in the height or the duration of the blood concentrations obtained following the administration of commercial penicillin and crystalline penicillin G.

Excretion studies revealed that when 100,000 units of penicillin G and penicillin X were administered intramuscularly, the former was found in the urine for eighteen hours, whereas the latter was present for at least twenty-four hours. The amounts recovered in the urine were 75 per cent of the penicillin G and 55 per cent of the penicillin X.

These observations agree essentially with those of other investigators. Ory et al.² found that the blood concentrations after the administration of penicillin X were significantly higher and more prolonged than those after the intramuscular injection of the same number of units of regular penicillin. Likewise, Welch and his co-workers³ noted that after the administration of 25,000 units of penicillin X and of regular penicillin the former product consistently maintained a higher blood concentration after two hours, and that the percentage of penicillin X recovered in the urine was smaller than that of penicillin G. Meads and his associates⁴ observed, however, that regular penicillin when administered orally yielded higher and more prolonged blood concentrations than penicillin X given by the same route, and they concluded that ordinary penicillin is less readily absorbed and excreted. No other reports on the absorption and excretion of crystalline penicillin G have been published.

In Vitro Sensitivity

One hundred and one strains of various bacteria, including staphylococci, streptococci, pneumococci, gonococci, meningococci and the influenza bacillus, were tested for sensitivity to penicillin X and to crystalline and commercial G fractions. The results of this study have been reported elsewhere.⁵ In brief, it may be stated that no difference was noted

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between the two penicillin G products. When the relative sensitivity of penicillins G and X was computed on the basis of weight, it was found that

fraction the organism also became more resistant to the other fraction, although not to the same extent. Similarly, several strains of bacteria that became

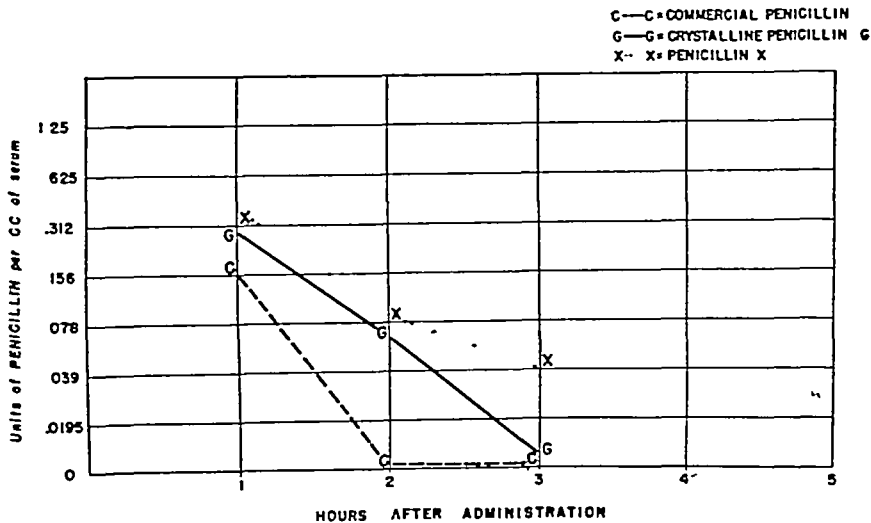


FIGURE 1 Median Values of Blood Concentrations Obtained following the Intramuscular Injection of 15,000 Units of Commercial Penicillin, Crystalline Penicillin G and Penicillin X

fifty-five strains were from two to sixteen times more sensitive to penicillin X, twenty-five were equally sensitive to both fractions, and twenty-one were two to four times more sensitive to penicillin G

resistant to fraction G in vivo were also more resistant to fraction X. Welch and his co-workers³ studied the in vitro action of penicillin X and commercial penicillin G

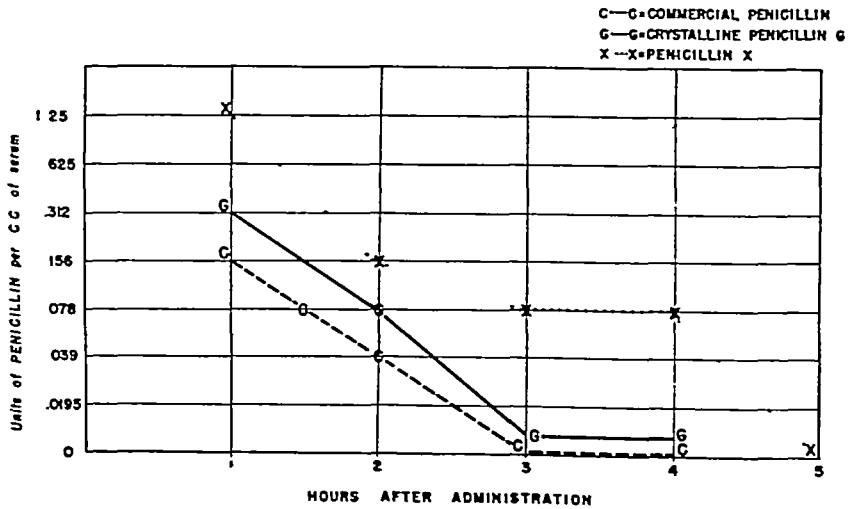


FIGURE 2 Median Values of Blood Concentrations Obtained following the Intramuscular Injection of 25,000 Units of Commercial Penicillin, Crystalline Penicillin G and Penicillin X

Further experiments were performed in which the resistance of various strains of organisms to one of these fractions was increased in vitro. In each instance, when the resistance was raised to one

on several strains of organisms, employing the unit as a measure of comparison. They noted that four strains of *Staphylococcus aureus* were equally sensitive to both fractions, but that one strain of *Kleb-*

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REFERENCES

- 1 Sub Committee on Civilian Rehabilitation, Baruch Committee on War and Postwar Physical Rehabilitation and Reconditioning, June 26, 1945 Report, (To be published)
- 2 Taylor, E. J. Teaching about America's handicapped *Civic Leader* 13 (No 11) 1-3, 1945

- 3 Medical Rehabilitation Division, United States Veterans Administration *What's My Score? (Handbook for patients with disabilities resulting from spinal-cord injuries)* 36 pp Washington, D.C. Government Printing Office, 1946
- 4 Deaver, G. C., and Brown, M. E. *Physical Demands of Daily Life: An objective scale for rating the orthopedically exceptional* 36 pp. New York Institute for Crippled and Disabled Studies in Rehabilitation No 1, 1945,
- 5 United States Emergency Management Office, War Manpower Commission *Physical Demands Analysis and Physical Capacities Appraisal* 37 pp Washington, D.C. Government Printing Office 1945

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to penicillin X, and that the remaining 50 per cent were either equally sensitive to both fractions or more sensitive to the G fraction. With the exception of a few strains, however, the differences in the sensitivity of the bacteria to either fraction were not great.

Therapeutic Activity

Various infections for which treatment with penicillin has been established were treated with the preparations discussed in an effort to determine whether there were any differences in their therapeutic action. Strict alternation was impossible because of the limited supply, and each product was therefore used when it was available. Table 1 presents the infections and the number of patients treated with each type of penicillin. Some of the cases in which penicillin X was used were discussed in greater detail in an earlier report.⁵ So far as could be determined, the three preparations were equally effective in the treatment of these infections. Although *in vitro* studies revealed certain variations in the sensitivity of the organisms to the types of penicillin, there was no obvious difference in the clinical response, either because the sensitivity of the organisms to each fraction was not varied enough to be of clinical significance or because the concentrations of penicillin obtained with the various regimes employed with all three products were higher than the sensitivity of the organisms, with the result that the lowest concentration was still bactericidal for the causative organism. The evidence available at present indicates that once a bactericidal concentration has been obtained a further increase in the concentration is not of added benefit.

Orv et al.² found that equivalent doses of penicillin X and commercial penicillin were equally effective in the treatment of pneumococcal pneumonia and other infections, such as staphylococcal bacteremia and severe cellulitis. These investigators considered penicillin X more effective than penicillin G in the treatment of gonorrhea when doses of 50,000 to 100,000 units were employed. Welch and his co-workers⁴ reported a 94 per cent cure rate in a group of 68 patients with gonorrhea who were given one dose of 25,000 units of penicillin X, whereas only 64 per cent of a group of 58 patients were cured with the same dose of commercial penicillin. The course of therapy in acute gonococcal urethritis is short, thus, when small doses are given, the prolonged duration of bactericidal activity of penicillin X may account for the observed superiority of this fraction.

There may be two exceptions to the general statement that penicillin X and penicillin G are equally effective therapeutically in all other infections. In the first place penicillin X may be given at less frequent intervals than equivalent doses of penicillin G without loss of the therapeutic effect. Secondly,

an occasional infection may be encountered, in which the causative organism is resistant to penicillin G but is sensitive to penicillin X. In such circumstances the greater sensitivity to penicillin X and the higher concentrations obtained with this product may become significant enough to warrant its use. Flippin and his associates⁹ encountered such a situation in a patient with bacterial endocarditis, who was cured with penicillin X after penicillin G had failed to control the infection.

Toxicity

Toxic reactions to penicillin, such as fever, nausea, vomiting and dermatitis, have been observed. Most investigators report a low incidence, whereas a few state that toxic manifestations are not at all infrequent.^{10, 11} All agree that the reactions are not serious, with few exceptions. The incidence in the series of patients under discussion was low — 7 cases in over 450 patients, almost all the reactions observed occurred in the early days of investigation when the products were impure. Six patients developed urticaria and one a fever. All the patients with urticaria had been treated with the impure commercial penicillin. Five developed symptoms during therapy, and the rash disappeared despite continuation of treatment. The sixth developed a generalized urticaria for forty-eight hours seven days after penicillin therapy had been discontinued. Delayed reactions to penicillin have been reported.^{12, 13} The remaining patient developed a fever while convalescing from pneumonia on the fifth day of treatment with crystalline penicillin G; there was no increase in the severity of the illness, and the temperature returned to normal when penicillin was discontinued. A repeat dose of penicillin did not, however, cause a rise in temperature.

All three products were instilled in the lumbar intrathecal space in the treatment of meningitis. There were no untoward reactions so long as the doses given were less than 100,000 units and the period of injections less than six weeks. Similarly, no unusual reactions were observed following the instillation of these three preparations into other serous cavities.

* * *

A comparison of the properties of penicillin X, crystalline penicillin G and commercial penicillin G demonstrated that penicillin X achieves and maintains higher blood concentrations than the injection of similar amounts of penicillin G, whereas there is no essential difference between the crystalline and commercial penicillin G in this respect.

Most bacteria are more sensitive to penicillin X than to penicillin G, but the difference is slight when they are compared on a weight basis.

The therapeutic effects of all three preparations are similar, with a few exceptions.

The incidence of toxic reactions was low and independent of the type of penicillin employed.

siella pneumoniae and one strain of *Bacillus cereus* were more sensitive to penicillin X, penicillin X was three to five times more effective than commercial penicillin in the protection of mice against ten thousand lethal doses of Type 1 pneumococci

than to commercial penicillin and that most strains of pneumococci and *Streptococcus viridans* were twice as sensitive to penicillin X when the unit was employed as a criterion of comparison. Recently, Hewitt and Pittman⁷ published the results

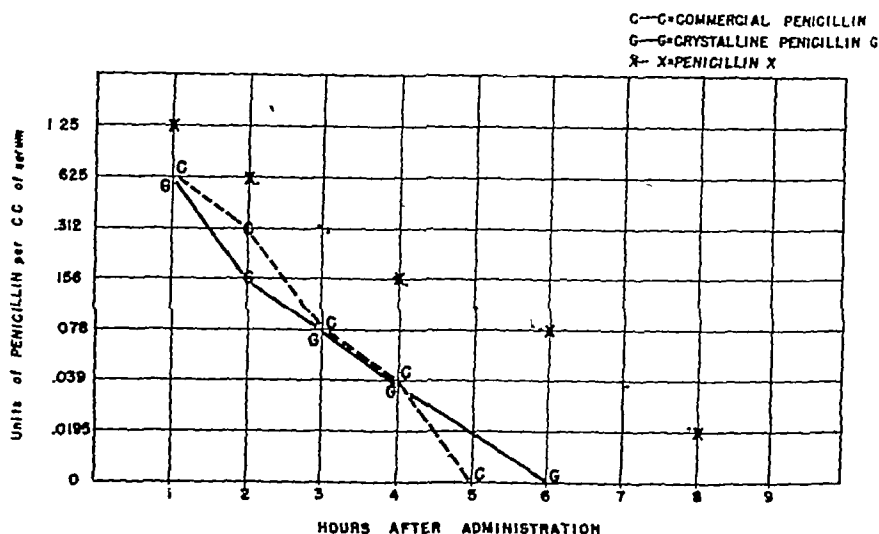


FIGURE 3 Median Values of Blood Concentrations following the Intramuscular Injection of 50,000 Units of Commercial Penicillin, Crystalline Penicillin G and Penicillin X

Libby and Holmberg⁶ observed that, with the exception of one strain of *Staph aureus* and one strain of *B subtilis*, the strains tested were more sensitive to penicillin X than to penicillin G, but

of a study of the comparison of the in vitro sensitivity of thirty-eight strains of *Haemophilus influenzae* to penicillins X and G. They found that most strains were more sensitive to penicillin X

TABLE 1 Results of the Treatment of Various Infections with Commercial Penicillin, Crystalline Penicillin G and Penicillin X

INFECTION	RESULTS WITH COMMERCIAL PENICILLIN		RESULTS WITH CRYSTALLINE PENICILLIN G		RESULTS WITH PENICILLIN X	
	IMPROVEMENT	NO IMPROVEMENT	IMPROVEMENT	NO IMPROVEMENT	IMPROVEMENT	NO IMPROVEMENT
Beta hemolytic streptococcus						
Scarlet fever	31	0	4	0	33	1
Erysipelas	1	0	1	0	3	0
Otitis media	8	0	5	0	6	1
Pharyngitis	11	0	4	0	11	0
<i>Streptococcus viridans</i> :						
Subacute bacterial endocarditis	15	3			1	2
Staphylococcus						
Bacteremia	7	1	1	1	0	1
Cellulitis and abscess	10	0	3	0	10	0
Arthritis	4	2	1	0	1	0
Pneumococcus						
Pneumonia	65	8	33	1	3	0
Meningitis	20	33	1	1	3	1
Gonococcus						
Urethritis, cervicitis and vaginitis	36	0	3	0	6	0
Arthritis	5	8*	3	0	4	0
Vincent's angina	4	1	1	0	2	1
Suppurative diseases of lung (bronchiectasis and lung abscess)	0	12	0	1	0	1
Empyema	2	8	0	1	0	1

*Seven patients were treated with doses that were subsequently determined to be inadequate

that the difference was less when the comparison was made on a weight rather than a unit basis. Ory et al² reported that most strains of Group A hemolytic streptococci, gonococci and meningococci were two to eight times more sensitive to penicillin X

and that this fraction was more effective in protecting the laboratory animals against the infection. A tabulation of the results of our studies and those of other investigators reveals that about 50 per cent of the strains of bacteria tested were more sensitive

ptics and to the sulfonamides, and the failure of emicillin therapy and radical sequestrectomy in the previous three-month period

The patients in the 4 cases described below were initially treated by thorough débridement and excision of necrotic tissue and poorly vascularized granulations, as well as by sequestrectomy or saucerization under Pentothal anesthesia. The wounds were, of course, well irrigated with physiologic saline solution. Tourniquets were not used in order that postoperative bleeding and venous stasis might be minimal, thus avoiding dilution of the topically applied streptomycin. In cases in which adequate hemostasis cannot be obtained with hot saline packs at the time of operation, it is far better to pack the wounds with nothing more than vaseline gauze pressure dressings for the first twenty-four or forty-eight hours before streptomycin therapy is begun. On the third or fourth postoperative day, the patient is returned to the operating room, where usually, without anesthesia, the wound can be gently irrigated with hot saline solution and the entire wound bed exposed without further ooze or active bleeding. Gela foam or fibrin foam soaked in streptomycin is then applied to the entire wound surface. The purpose in using gela foam is twofold: to ensure that the entire wound surface is in contact with the streptomycin applied locally, and to promote healing and granulation.

The local dosage of streptomycin was arbitrarily set at about 150,000 units daily, whereas 200,000 units was administered intramuscularly every three hours for patients receiving combined therapy. At present we are treating wounds more grossly infected than those described below with dosages as high as 500,000 units intramuscularly every three hours, and the results have been excellent. Quite often we have observed that *Ps. aeruginosa* is highly resistant to streptomycin both in vivo and in vitro, but this obstacle is easily overcome by the substitution of a 1 per cent acetic acid solution for twenty-four hours. Before further streptomycin therapy is given, the wound should be thoroughly irrigated with saline solution, since streptomycin is rendered inactive in an acid medium.

CASE REPORTS

CASE 1 On February 18, 1944, a 37-year-old private was struck by an automobile while crossing a street in a mid-western state. He was taken to a hospital, where a diagnosis of compound and comminuted complete fractures of the left tibia and fibula, at the junction of the middle and proximal thirds, was made. The left leg was put in plaster from toes to groin after closed reduction of the fracture, following which the general condition was excellent. On March 7 the patient was transferred to a larger hospital, where it was learned that there was about 10 or 15° of posterior bowing of the tibial fracture and about 50 per cent contact between the fracture ends. At that time there was no definite callus formation. Laboratory examinations were essentially negative.

During the stay at the second hospital, the cast was wedged at the fracture site, and posterior and medial angulations were corrected. This change was corroborated by x-ray studies. Immobilization in the plaster cast was continued

until April 26, when the cast was removed and gross motion at the fracture site was observed on physical examination. The denuded skin surfaces about the fracture also remained unhealed. A new long leg cast was applied to the involved extremity, and on July 21 the patient was transferred to the Cushing General Hospital.

At the time of admission there was no clinical evidence of union. Because of the poor condition of the skin of the involved extremity, operation was postponed, and the suppurative skin wounds were treated with sulfadiazine soaks, sulfanilamide powder and penicillin dressings. A sliding type of bone graft was carried out on October 5, but postoperatively the wound broke down and drained copious amounts of thick yellow pus in spite of combined penicillin therapy. On January 2, under intravenous anesthesia, the infected tibial graft was removed, the cavity and surrounding necrotic bone were curetted, and the wound was packed with penicillin-soaked gauze. At that time a large number of colonies of *Ps. aeruginosa* were observed in plate cultures from the wound. In May, since the patient's condition was essentially unchanged, a second sequestrectomy was carried out but drainage continued unabated. In August the wound was sufficiently clean so that it was covered with a dermatome graft, of which 80 per cent took. Subsequent x-ray films, however, showed progressive bone destruction, and on February 5, 1946 a thorough saucerization of the proximal end of the tibia was performed. The postoperative course was stormy; the entire extremity became distended and painful, and the wound drained considerably in spite of Azochloramide dressings. Late in February, sulfanilamide irrigations were initiated with poor results. Acriflavine also proved to be of no value.

In early March culture reports indicated that the predominant organisms in the discharge from the extremity were *Pr. vulgaris* and *Ps. aeruginosa*. In vitro studies showed that the organisms were sensitive to a solution of streptomycin containing 32 units per cubic centimeter. On March 11, under Pentothal anesthesia the defect on the anterior aspect of the left leg was débrided, the skin edges were excised, and the wound was irrigated with physiologic saline solution and then packed with fibrin foam to which 150,000 units of streptomycin had been added. Starting with this date, 200,000 units of streptomycin was administered intramuscularly every 3 hours. In addition to the above therapy the wound was irrigated three times daily with 10 cc of streptomycin, or a total daily equivalent of 150,000 units. Two days later a large amount of autolyzed fibrin foam was removed from the depths of the wound, which was then irrigated with 500 cc of physiologic saline solution. An excellent granulating surface was presented at that time. The entire area, however, was again resurfaced with fibrin foam to which 150,000 units of streptomycin had been added. Local and intramuscular therapy was continued as described above. On the 5th postoperative day local streptomycin therapy was discontinued and irrigation with 1 per cent acetic acid instituted, since the contaminant had become resistant to streptomycin. On the 7th day after operation, under Pentothal anesthesia, the left lower extremity was thoroughly irrigated with physiologic saline solution and a dermatome graft applied to about 90 per cent of the defect. The remaining denuded areas were covered with pinch grafts. Intramuscular doses of streptomycin were continued up to the 7th day following the second operation. The graft was a complete success.

Three months later x-ray films revealed excellent callus formation about the sites of the fractures of the tibia and fibula, and a leg brace was ordered.

CASE 2 On January 30, 1945, a 22-year-old soldier was wounded in action in Germany, sustaining a rifle-bullet wound of the left forearm and a fracture of the left radius, with complete paralysis of the left radial nerve. He was treated at a battalion aid station, where the upper extremity was splinted and dressed, and was subsequently sent to a collecting company, from which he was evacuated to a general hospital. Initially, the wound was débrided, and a plaster cast applied to the forearm. In April because of loss of tissue substance about the middle third of the left radius, a skin flap to the left forearm was carried out, and a Roger-Anderson splint applied to immobilize the bone fragments. Following this procedure the patient was evacuated to the Zone of the Interior.

It is concluded that in practically all infections caused by penicillin-sensitive organisms there is no obvious clinical difference between the effectiveness of the penicillin X and G fractions

REFERENCES

- 1 Committee on Medical Research, OSRD, Washington and the Medical Research Council, London Chemistry of penicillin *Science* 102 627-629 1945
- 2 Ory, E M, Meads M, and Finland, M Penicillin X comparison with penicillin G with respect to sensitivity of pathogenic organisms and serum levels *J A M A* 129 257-261, 1945
- 3 Welch, H, Putnam, L E, Randall W A, and Herwick, R P Penicillin X successful treatment of gonorrhea with single intramuscular injection *J A M A* 126 1024, 1944
- 4 Meads, M, Ory, E M, and Finland, M Oral penicillin X *Science* 103 501, 1946
- 5 Dowling, H F, Hirsh, H L, and O'Neil C B Studies on bacteria developing resistance to penicillin fractions X and G in vitro and in patients under treatment for bacterial endocarditis *J Clin Investigation* 25 665-672, 1946
- 6 Libby R L and Holmberg N L Activity of penicillins G and X *in vitro Science* 102 303, 1945.
- 7 Hewitt, W L., and Pittman, M Antibacterial action of penicillin, penicillin X, and streptomycin on *Hemophilus influenzae* *Pub Health Rep* 61 768-778 1946
- 8 Hirsh H L, Dowling, H F, and Sweet, L K Treatment of various infections with penicillin X with preliminary note on value of penicillin X in scarlet fever *Ann Int Med* 25 78-87 1946.
- 9 Flippin, H F, Maycock, R L, Murphy, F D, and Wolferth, C C Penicillin in treatment of subacute bacterial endocarditis preliminary report on twenty cases treated over one year ago *J A M A* 129 841-843, 1945
- 10 Kolodny, M H, and Denhoff, E. Reactions in penicillin therapy *J A M A* 130 1058-1061 1946
- 11 Cormia, F E, Jacobsen, L Y, and Smith, E L Reactions to penicillin *Bull U S Army M Dept* 4 694-702, 1945
- 12 Price D E, McNairy D J and White E L Severe asthma delayed sensitization to penicillin *J A M A* 128 183, 1945
- 13 Conferences on Therapy Department of Pharmacology and Medicine, Cornell University Medical College and the New York Hospital November 30 1944 Penicillin *New York State J Med* 45 1875-1883 1945

TREATMENT OF CHRONIC OSTEOMYELITIS WITH STREPTOMYCIN

A PRELIMINARY REPORT

MAJOR TIMOTHY A LAMPHIER, M C, A U S, * AND CAPTAIN CHARLES CASHMAN, M C, A U S †

FRAMINGHAM, MASSACHUSETTS

AT THE time of this writing no data on streptomycin as a specific agent in the treatment of chronic osteomyelitis had been reported in the literature. The results in the cases reported below are considered sufficiently successful to justify publication.

In World War II a major problem in the treatment of compound comminuted fractures was the resultant chronic infection. There is no doubt that penicillin played a great role in either eradicating or localizing infectious processes. Certainly, the bacteremias and septicemias following compound bone injuries so characteristic of World War I were the exception rather than the rule in World War II. Many soldiers, however, returned to the Zone of the Interior with bone injuries infected with mixed bacteria that failed to respond to penicillin therapy, even though thorough sequestrectomy and débridement had been carried out at overseas installations.

As Abraham and Chain† have aptly stated, the presence of gram-negative bacteria in a wound with mixed infection often inactivates penicillin by the production of the penicillin-inhibiting enzyme penicillinase. Certainly, the majority of gram-negative organisms found in the wounds of patients in the osteomyelitis section of the Cushing General Hospital can be classified as nothing more than secondary contaminants, and as such were not of too great significance from a purely pathological standpoint. In the main, these secondary contaminants

were *Pseudomonas aeruginosa*, *Proteus vulgaris* and *Aerobacter aerogenes*. A careful study of the case histories, however, demonstrated that the organisms markedly prolonged wound healing. The usual local antiseptics, such as Azochloramid, acriflavine and Dakin's solution, which had previously been resorted to when penicillin failed in the treatment of chronic osteomyelitis, were of almost negligible or, at the most, highly questionable value in the so-called "open treatment" of chronic bone infections. One cannot underestimate the presence of pieces of clothing, shell fragments, necrotic tissue and sequestra as causative factors for prolonged drainage with bone injuries. The value of x-ray examination in ruling out the presence of many foreign bodies should not obscure the fact that nonopaque materials, such as small pieces of wood, glass and fragments of clothing, are often responsible for persistent drainage. Rather frequently, sequestra are so small or so obscured by adjacent and viable eburnated bone that they are not detected in routine x-ray plates. Of some value in the location of necrotic material is the placing of probes or the introduction of a contrast medium such as Diodrast in sinus tracts, followed by routine x-ray examination, but even these aids are not applicable in every case.

Prior to treating any cases of bone infection with streptomycin, we have considered the following factors: the predominant type of organisms cultured from the wound, in vitro studies repeated on at least three separate occasions during the week prior to the onset of therapy, the duration of the drainage, the failure of the drainage to respond to local anti-

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‡Abraham E P, and Chain E. Enzyme from bacteria able to destroy penicillin *Nature* London 146 837, 1940

otics and to the sulfonamides, and the failure of penicillin therapy and radical sequestrectomy in the previous three month period.

The patients in the 4 cases described below were usually treated by thorough débridement and excision of necrotic tissue and poorly vascularized granulations, as well as by sequestrectomy or saucerization under Pentothal anesthesia. The wounds were, of course, well irrigated with physiologic saline solution. Tourniquets were not used in order that postoperative bleeding and venous stasis might be minimal, thus avoiding dilution of the topically applied streptomycin. In cases in which adequate hemostasis cannot be obtained with hot saline packs at the time of operation, it is far better to pack the wounds with nothing more than vaseline gauze pressure dressings for the first twenty-four or forty-eight hours before streptomycin therapy is begun. On the third or fourth postoperative day, the patient is returned to the operating room, where, without anesthesia, the wound can be gently irrigated with hot saline solution and the entire wound bed exposed without further ooze or active bleeding. Gela foam or fibrin foam soaked in streptomycin is then applied to the entire wound surface. The purpose in using gela foam is twofold: to ensure that the entire wound surface is in contact with the streptomycin applied locally, and to promote healing and granulation.

The local dosage of streptomycin was arbitrarily set at about 150,000 units daily, whereas 200,000 units was administered intramuscularly every three hours for patients receiving combined therapy. At present we are treating wounds more grossly infected than those described below with dosages as high as 500,000 units intramuscularly every three hours and the results have been excellent. Quite often we have observed that *Ps. aeruginosa* is highly resistant to streptomycin both in vivo and in vitro, but this obstacle is easily overcome by the substitution of a 1 per cent acetic acid solution for twenty-four hours. Before further streptomycin therapy is given, the wound should be thoroughly irrigated with saline solution, since streptomycin is rendered inactive in an acid medium.

CASE REPORTS

CASE 1 On February 18, 1944, a 37-year-old private was struck by an automobile while crossing a street in a midwestern state. He was taken to a hospital, where a diagnosis of compound and comminuted complete fractures of the left tibia and fibula, at the junction of the middle and proximal thirds, was made. The left leg was put in plaster from toes to groin after closed reduction of the fracture, following which the general condition was excellent. On March 7 the patient was transferred to a larger hospital, where it was learned that there was about 10 or 15° of posterior bowing of the tibia and about 50 per cent contact between the fracture ends. At that time there was no definite callus formation. Laboratory examinations were essentially negative.

During the stay at the second hospital, the cast was wedged at the fracture site, and posterior and medial angulations were corrected. This change was corroborated by x-ray studies. Immobilization in the plaster cast was continued

until April 26 when the cast was removed and gross motion at the fracture site was observed on physical examination. The denuded skin surfaces about the fracture also remained unhealed. A new long leg cast was applied to the involved extremity and on July 21 the patient was transferred to the Cushing General Hospital.

At the time of admission there was no clinical evidence of union. Because of the poor condition of the skin of the involved extremity, operation was postponed, and the suppurative skin wound were treated with sulfadiazine soaks, sulfanilamide powder and penicillin dressings. A sliding type of bone graft was carried out on October 5, but postoperatively the wound broke down and drained copious amounts of thick yellow pus in spite of combined penicillin therapy. On January 2 under intravenous anesthesia, the infected tibial graft was removed, the cavity and surrounding necrotic bone were curetted, and the wound was packed with penicillin-soaked gauze. At that time a large number of colonies of *Ps. aeruginosa* were observed in plate cultures from the wound. In May since the patient's condition was essentially unchanged a second sequestrectomy was carried out but drainage continued unabated. In August the wound was sufficiently clean so that it was covered with a dermatome graft of which 80 per cent took. Subsequent x-ray films, however, showed progressive bone destruction and on February 5, 1946 a thorough saucerization of the proximal end of the tibia was performed. The postoperative course was stormy, the entire extremity became distended and painful, and the wound drained considerably in spite of Neochloramide dressings. Late in February, sulfadiazine irrigations were initiated with poor results. Acetic acid also proved to be of no value.

In early March culture reports indicated that the predominant organisms in the discharge from the extremity were *Ps. vulgaris* and *Ps. aeruginosa*. In vitro studies showed that the organisms were sensitive to a solution of streptomycin containing 32 units per cubic centimeter. On March 11, under Pentothal anesthesia the defect in the anterior aspect of the left leg was debrided, the sloughs were excised and the wound was irrigated with physiologic saline solution and then packed with fibrin foam to which 1 (1000) units of streptomycin had been added. Starting with this date, 200,000 units of streptomycin was administered intramuscularly every 3 hours. In addition to the above therapy the wound was irrigated three times daily with 10 cc of streptomycin, or a total daily equivalent of 150,000 units. Two days later a large amount of autolyzed fibrin foam was removed from the depths of the wound which was then irrigated with 500 cc of physiologic saline solution. An excellent granulating surface was presented at that time. The entire area, however, was again resurfaced with fibrin foam to which 150,000 units of streptomycin had been added. Local and intramuscular therapy was continued as described above. On the 5th postoperative day local streptomycin therapy was discontinued, and irrigation with 1 per cent acetic acid instituted, since the contaminant had become resistant to streptomycin. On the 7th day after operation, under Pentothal anesthesia, the left lower extremity was thoroughly irrigated with physiologic saline solution and a dermatome graft applied to about 90 per cent of the defect. The remaining denuded areas were covered with pinch grafts. Intramuscular doses of streptomycin were continued up to the 7th day following the second operation. The graft was a complete success.

Three months later x-ray films revealed excellent callus formation about the sites of the fractures of the tibia and fibula, and a leg brace was ordered.

CASE 2 On January 30, 1945, a 22-year-old soldier was wounded in action in Germany, sustaining a rifle bullet wound of the left forearm and a fracture of the left radius, treated at a battalion aid station, where the upper extremity was splinted and dressed, and was subsequently sent to a collecting company, from which he was evacuated to a general hospital. Initially, the wound was débrided, and a flap of tissue substance about the middle third of the left radius, Anderson splint applied to immobilize the bone fragments. Following this procedure the patient was evacuated to the Zone of the Interior.

It is concluded that in practically all infections caused by penicillin-sensitive organisms there is no obvious clinical difference between the effectiveness of the penicillin X and G fractions

REFERENCES

- 1 Committee on Medical Research, OSRD, Washington and the Medical Research Council, London *Chemistry of penicillin* *Science* 102:627-629 1945
- 2 Ory, E. M., Meads, M., and Finland, M. Penicillin X comparison with penicillin G with respect to sensitivity of pathogenic organisms and serum levels *J A M A* 129:257-261, 1945
- 3 Welch, H., Putnam, L. E., Randall, W. A., and Herwick, R. P. Penicillin X, successful treatment of gonorrhea with single intramuscular injection *J A M A* 126:1024, 1944
- 4 Meads, M., Ory, E. M., and Finland, M. Oral penicillin X *Science* 103:501 1946
- 5 Dowling, H. F., Hirsch, H. L., and O'Neil, C. B. Studies on bacteria developing resistance to penicillin fractions X and G in vitro and in patients under treatment for bacterial endocarditis *J Clin Investigation* 25:665-672 1946
- 6 Libby, R. L., and Holmberg, N. L. Activity of penicillin G and X *in vitro* *Science* 102:303, 1945.
- 7 Hewitt, W. L., and Pittman, M. Antibacterial action of penicillin, penicillin X, and streptomycin on *Hemophilus influenzae* *Pub. Health Rep* 61:768-778 1946
- 8 Hirsch, H. L., Dowling, H. F., and Sweet, L. K. Treatment of various infections with penicillin X, with preliminary note on value of penicillin X in scarlet fever *Ann Int Med* 25:78-87 1946
- 9 Flippin, H. F., Maycock, R. L., Murphy, F. D., and Wollerich, C. C. Penicillin in treatment of subacute bacterial endocarditis: preliminary report on twenty cases treated over one year ago *J A M A* 129:841-843 1945
- 10 Kolodny, M. H., and Denhoff, E. Reactions in penicillin therapy *J A M A* 130:1058-1061, 1946
- 11 Cormia, F. E., Jacobsen, L. Y., and Smith, E. L. Reactions to penicillin *Bull U S Army Med Dept* 4:694-702, 1945
- 12 Price, D. E., McNairy, D. J., and White, E. L. Severe asthma, delayed sensitization to penicillin *J A M A* 128:183, 1945
- 13 Conferences on Therapy. Department of Pharmacology and Medicine, Cornell University Medical College and the New York Hospital. November 30 1944. Penicillin. *New York State J Med* 45:1875-1883, 1945

TREATMENT OF CHRONIC OSTEOMYELITIS WITH STREPTOMYCIN

A PRELIMINARY REPORT

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AT THE time of this writing no data on streptomycin as a specific agent in the treatment of chronic osteomyelitis had been reported in the literature. The results in the cases reported below are considered sufficiently successful to justify publication.

In World War II a major problem in the treatment of compound comminuted fractures was the resultant chronic infection. There is no doubt that penicillin played a great role in either eradicating or localizing infectious processes. Certainly, the bacteremias and septicemias following compound bone injuries so characteristic of World War I were the exception rather than the rule in World War II. Many soldiers, however, returned to the Zone of the Interior with bone injuries infected with mixed bacteria that failed to respond to penicillin therapy, even though thorough sequestrectomy and débridement had been carried out at overseas installations.

As Abraham and Chain‡ have aptly stated, the presence of gram-negative bacteria in a wound with mixed infection often inactivates penicillin by the production of the penicillin-inhibiting enzyme penicillinase. Certainly, the majority of gram-negative organisms found in the wounds of patients in the osteomyelitis section of the Cushing General Hospital can be classified as nothing more than secondary contaminants, and as such were not of too great significance from a purely pathological standpoint. In the main, these secondary contaminants

were *Pseudomonas aeruginosa*, *Proteus vulgaris* and *Aerobacter aerogenes*. A careful study of the case histories, however, demonstrated that the organism markedly prolonged wound healing. The usual local antiseptics, such as Azochloramid, acriflavin and Dakin's solution, which had previously been resorted to when penicillin failed in the treatment of chronic osteomyelitis, were of almost negligible or at the most, highly questionable value in the so-called "open treatment" of chronic bone infections. One cannot underestimate the presence of pieces of clothing, shell fragments, necrotic tissue and sequestra as causative factors for prolonged drainage with bone injuries. The value of x-ray examination in ruling out the presence of many foreign bodies should not obscure the fact that nonopaque materials, such as small pieces of wood, glass and fragments of clothing, are often responsible for persistent drainage. Rather frequently, sequestra are so small or so obscured by adjacent and viable eburnated bone that they are not detected in routine x-ray plates. Of some value in the location of necrotic material is the placing of probes or the introduction of a contrast medium such as Diodrast in sinus tracts, followed by routine x-ray examination, but even these aids are not applicable in every case.

Prior to treating any cases of bone infection with streptomycin, we have considered the following factors: the predominant type of organisms cultured from the wound, in vitro studies repeated on at least three separate occasions during the week prior to the onset of therapy, the duration of the drainage, the failure of the drainage to respond to local anti-

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course was normal, the dressings being removed on the 10th day after operation when the skin graft was found to have taken well. Because of an unstable right ankle joint due to the destruction of many of the tendinous structures in the lower leg, on February 8 an intramedullary sliding type of ankle fusion was carried out on the right leg.

On February 13, following the ankle fusion, x-ray films revealed a sliding bone graft extending from the distal end of the tibia into the astragalus. Other bone detail was obscured by plaster. (During the following month x-ray study showed periosteal elevation along the shaft of the tibia beginning about 5 cm proximal to the distal end of the shaft and extending upward for a distance of 25 cm, associated with the changes were areas of decreased density from the cortex of the tibia that were consistent with bone destruction.)

On February 15 the cast was split because of extreme pain and swelling with cyanosis of the toes. The patient continued to run a moderately elevated temperature, and the wound was therefore inspected, a breakdown of the skin over the lateral malleolus, with purulent serous drainage, was found. Despite irrigation with 1 per cent sulfadiazine solution, the entire anterior aspect of the ankle joint broke down and drained profusely.

On February 20 streptomycin sensitivity reports on organisms cultured from the wound were recorded as follows: *A. aerogenes*, sensitive to 2 units per cubic centimeter, hemolytic *Staphylococcus aureus*, sensitive to 8 units per cubic centimeter, and beta-hemolytic streptococcus, sensitive to 32 units per cubic centimeter. During March, the blood plasma protein was 7.2 gm per 100 cc. Subsequent cultures taken from the wound of the right leg during March were reported as showing *Ps. aeruginosa*, *A. aerogenes*, beta-hemolytic streptococcus and hemolytic *Staph. aureus*. On April 5 the *Ps. aeruginosa* was found to be resistant to 250 units and the hemolytic *Staph. aureus* sensitive to 0.5 units per cubic centimeter of streptomycin. On March 5 daily topical treatment of the wound with 15,000 units of streptomycin was begun. By March 21 the wound had become grossly clean, and the area of the tibia that had previously been exposed was covered with granulation tissue. On March 25 the wound was covered with a split-thickness graft taken from the left thigh, and a vaseline pressure dressing was applied. About 90 per cent of the graft was viable on the 10th postoperative day. During the following weeks a few pinch grafts were used to cover the remaining denuded

areas. Two months later the wound remained well healed. The original fracture of the mid-tibia and fibula had healed without further treatment.

Although the results obtained in these 4 cases were gratifying, it should be emphasized that the evaluation of any method of therapy in cases of chronic osteomyelitis cannot be final until a period of years has elapsed, since in the past there has been recurrence in many cases that have been thought to have been "cured."

Incidentally, the discomfort of repeated injections was successfully alleviated by combining solutions of the drug with procaine.

SUMMARY

Four cases of chronic osteomyelitis are presented 3 of which were treated with combined intramuscular and local streptomycin therapy and 1 with local applications alone. An obvious advantage of the combined therapy is that such procedures as skin grafting and secondary closure can be carried out in a much shorter time. One is easily guided by the success of in vitro studies prior to using streptomycin. No toxic reactions were observed in this series.

BIBLIOGRAPHY

- Jones D. Metzger H. J. Schatz, A., and Waksman S. A. Control of gram negative bacteria in experimental animals. *Science* 100:10-10² 1944
- Meleney F. L., Johnson B. A., Pulaski, E. J., and Colonna F. Treatment of mixed infections with penicillin. I. With special reference to adjuvant action of parachlorophenol. *J. A. M. A.* 130:121-124 1946
- Waksman S. A., Bugie E., and Schatz A. Isolation of antibiotic substances from soil micro-organisms with special reference to streptomycin and streptomycin. (Mayo Foundation lecture.) *Proc. Soc. Med., Mayo Clin.* 19:537-548 1944
- Woodruff H. B., and Foster J. W. Microbiological aspects of penicillin VII. Bacterial penicillinase. *J. Bact.* 49:7-17 1945

On entry to a general hospital, x-ray examination disclosed a 3-cm gap in the proximal portion of the lower half of the left radius. There was a sequestrum adjacent to the proximal end of the distal fragments. No other abnormalities were noted besides the nonunion and marked osteoporosis. Shortly after admission, the sequestrum was removed. On October 1 a bone graft to the left radius was carried out, the left tibia being used as a donor site, but the graft broke down and thick, purulent material started to drain from the anterior aspect of the forearm.

At the time of his admission to the Cushing General Hospital, in January, 1946, the diagnosis was a compound, complete fracture of the left radius, with osteomyelitis and necrosis of the bone graft. On February 8 the bone graft was removed and sinus tracts excised, an indwelling catheter being inserted for subsequent penicillin therapy. In spite of this procedure and subsequent penicillin irrigations, as well as a course of penicillin intramuscularly, two sinus tracts over the volar aspects of the left forearm continued to drain a heavy, thick, purulent material.

Blood studies and urinalyses were within normal limits. On February 14, cultures of the material taken from the draining sinus tracts of the left forearm were reported as showing *Pr. vulgaris*, and the organisms were found to be sensitive to 0.5 units of streptomycin per cubic centimeter. On February 25, under general anesthesia, the sinus tracts of the left forearm were excised, and all necrotic tissue was debrided, hemostasis was obtained, and the wound was packed with fibrin foam soaked in streptomycin. At that time 200,000 units of streptomycin was given intramuscularly, every 3 hours. On the 1st postoperative day local irrigations with 150,000 units of streptomycin were initiated, in addition to the intramuscular therapy. Four days later, since cultures had proved the wound to be clean, a secondary closure was carried out, steel wire being employed as a suture material. Streptomycin continued to be injected intramuscularly (200,000 units every 3 hours) for a total of 7 days, at the end of which the sutures were removed. A few stitch abscesses developed at the periphery of the wound, but these were treated with streptomycin dressings and healed within a 5-day period. The forearm was then encased in plaster and remained well healed for the next 3 months, at the end of which x-ray examination revealed excellent callus formation about the radial bone fragments.

CASE 3 On March 28, 1945, a 21-year-old soldier was wounded in action in Germany, sustaining a penetrating wound of the left hand. Shrapnel entered the dorsum of the hand, fracturing the 2nd and 3rd metacarpal bones, and x-ray films subsequently showed a marked loss of bone substance. The patient was treated in a nearby evacuation hospital, where débridement was carried out, and was then transferred to a general hospital in Paris, where the wound was secondarily closed. On June 14 he was evacuated to the Zone of the Interior, arriving at the Cushing General Hospital on August 13.

On entry, examination of the left hand showed a depressed adherent scar, with a small granulating area in its center, on the dorsal surface over the proximal ends of the 2nd and 3rd metacarpals. The index and middle fingers were about 2 cm short, with obvious bone loss of the corresponding metacarpals. The extensor tendons to the index finger had been destroyed, but that to the middle finger was present. The flexor tendons were functioning normally but through a reduced range because of the adherent scar dorsally, and because of stiffening of the metacarpophalangeal joint secondary to immobilization. The nerves were intact. The diagnosis was a compound, comminuted fracture of the 2nd and 3rd metacarpals, with loss of bone substance.

On August 21 it was decided that, since there was not an appreciable amount of skin over the dorsum of the hand, a small abdominal-flap operation should be carried out, to prepare the finger for lengthening at a later date. On October 11 an abdominal flap was attached to the left hand, and 3 weeks later the flap was detached and inserted.

On January 15, 1946, it was suggested that since the flap on the dorsum of the hand was in good condition, the patient should be transferred to the Hand Section for a metacarpal bone graft. On February 1 the bone graft was carried out, the metacarpal defect of the index finger being filled in and the tibia being utilized as a donor site. Three days postoperatively the patient began to run a septic temperature

and complained of severe pain over the dorsum of the hand. The cast was therefore removed, and the wound was found to be grossly septic. On February 8 cultures of the material draining from the dorsum of the hand were reported as showing *A. aerogenes*, and a few days later these bacteria were found to be sensitive to 0.5 units of streptomycin per cubic centimeter. Since the wound continued to drain profusely in spite of penicillin administered intramuscularly and locally, the ulnar aspect of the abdominal flap on the dorsum of the hand was incised and the surrounding necrotic tissue excised on February 26. The incision was carried down to the dorsum of the bone graft, which appeared to be viable. After thorough irrigation with physiologic saline solution and careful control of excessive bleeding, the wound was packed with fibrin foam soaked in streptomycin. A vaseline dressing was applied to the wound, and the hand was set up in so-called "cock-up position" with the aid of a splint. Post operatively, 50,000 units of streptomycin was injected locally into the wound each day, and 200,000 units was administered intramuscularly every 3 hours. On March 1 specimens were taken from the wound for culture, as well as a small amount of fibrin foam for streptomycin sensitivity tests. Since the wound still appeared to be septic, it was thoroughly irrigated with physiologic saline solution and streptomycin, all remnants of the fibrin foam were removed, and a partial closure was carried out with No. 40 cotton suture, except in the center of the incision, where a small piece of Penrose tubing was placed. Two days later the rubber drain was removed, since the wound appeared to be clean. For a total of 7 days 200,000 units of streptomycin was continued every 3 hours. The skin flap healed rapidly.

Fifteen days later, when the patient was to have a plaster cast applied, the skin flap over the dorsum of the left hand again broke down, draining a small amount of yellow purulent material. Cultures of the drainage were reported as showing *Escherichia coli*, sensitive to 32 units per cubic centimeter of streptomycin, and *A. aerogenes*, sensitive to 4 units per cubic centimeter. Local irrigations consisting of 30,000 units of streptomycin were initiated at once and continued for a period of 10 days, at the end of which the wound had healed spontaneously. Three months later the wound remained closed, and x-ray films revealed excellent callus formation about the metacarpal graft.

CASE 4 On February 7, 1945, a 20-year-old soldier was injured in Werben, Germany, by a land mine, sustaining injuries to the left thigh, leg and foot and to the right buttock, knee, leg, and foot. These injuries included compound and comminuted complete fractures of the right tibia and fibula, as well as paralysis of the right peroneal nerve. The wounds were debrided, and the right lower extremity was splinted at a first-aid station. On arrival at an evacuation hospital, the right leg was encased in a mid-thigh plaster cast, following which the patient was evacuated to the Zone of the Interior and admitted to a general hospital on April 10. At that time a sequestrectomy was performed on the right tibia, but since this procedure did not bring about satisfactory results, a thorough saucerization of the right tibia was carried out early in June. Approximately 3 weeks later, small, deep, pinch grafts were applied to the saucerized area with good results. In September the patient was transferred to the Cushing General Hospital for definitive treatment.

During his confinement, blood and serologic studies and urinalyses were reported as negative. X-ray films of the right lower leg showed a comminuted fracture of the mid-shaft of both bones, with loss of bone substance on the outer anterior surface of the tibia and with numerous, multiple foreign bodies in the soft tissues at the site of the fracture.

In early October the long leg cast on the right lower extremity, in which the patient had been admitted, was bivalved, and a small saucerized area was evident on the anterior aspect of the right leg at the level of the fracture site. At the upper end of the cavity, which was filled with small deep grafts, there was a small draining sinus. Since penicillin dressings were of no avail, on October 22, under intravenous anesthesia, the tibial wound was explored and saucerized, loose bone fragments removed and the area covered with a pressure dressing in which a catheter was incorporated for penicillin instillation. On October 31, under intravenous anesthesia, a dermatome graft was removed from the right thigh and sutured in position over the granulating area of the right tibia. Pressure dressings were applied. The postoperative

short-circuiting in a previously colourful personality certainly is preferable to an incurable psychotic misery

It is generally agreed that the operation leaves the patient with a definite loss of initiative and a shallowness of affect. Other symptoms or tendencies, persistent in a large percentage of cases, include euphoria, procrastination, facetiousness, increased appetite, laziness and tactlessness.⁴ This rather alarming list of characteristics does not, however, prevent many patients from carrying on with work. Berliner et al.⁸ describe a woman, a librarian, who was not able to do simple work in the hospital library a few months after her operation because her powers of retention were greatly impaired. Three months later, however, she took a job in a public library, where she had worked satisfactorily for eighteen months at the time of the report.

Freeman and Watts³ present the following description of the results of leukotomy:

Patients who have made a satisfactory recovery are far from inanimate clods. They are cheerful, friendly, uncomplaining, outspoken, buoyant, for the most part. They fall in with the mood of their companions, are quick to follow suggestions and are not embarrassed, glum or self-conscious. They take an active interest in everything that goes on about them, read the papers, attend movies, work regularly and play games with intelligence and foresight. With them the emotional component of foresight and insight is sufficient for meeting external situations of moderate complexity. Many patients have a more or less complete amnesia for the whole psychotic period.

Hofstatter and his associates⁹ report that, at the time of writing, 14 in a series of 100 patients who underwent leukotomy were regularly employed, 4 of them for the first time in their lives. Another 12 were carrying the full responsibility of house-keeping.

The question of a permanent deficit in intellectual functions following leukotomy has not had thorough study because of the lack, in general, of premorbid data on these capacities in the patients concerned. Hofstatter et al.⁹ state that the intellectual assets were not diminished in their cases. Frank⁷ observes that in a series of 200 cases, except for 16 patients over fifty-five years of age, no impairment of cognition or intellectual deficit was observed a year after the operation. Halstead, Carmichael and Bucy¹⁰ developed a battery of tests designed for assessing the so-called "biologic intelligence." This term, in contrast to the standardized psychometric tests, is explained as follows:

Psychiatry, and for that matter the whole field of biology, has long felt the need for a conception of intelligence more closely related to the clinically observed capacities of the individual for general adaptive behavior.

The tests were given to 8 carefully selected patients before and after prefrontal lobotomy. The guarded conclusions of the authors were that the biologic intelligence, as reflected by an impairment index, did not appear to be altered significantly by prefrontal

lobotomy, and that little is known concerning the behavioral effects of this operation.

The best results from leukotomy are obtained in the long-standing depressions, particularly of the involuntional and agitated types, in obsessive-ruminative-tension states and in certain types of schizophrenia. The more the patient is tense, anxious, emotionally disturbed, the more he is, in effect, fighting his disease, and the better are the chances of relief by this operation. Frank⁷ considers the indications for leukotomy strongest in patients with a colorful personality, beneath whose psychotic symptoms a depth of emotional response can be discerned. The first 75 of his 200 cases were selected exclusively because of distressing and permanently disturbing hallucinations, unmanageable aggressiveness, unceasing melancholic agitation, constant unrelieved anxiety due to delusional experiences or organ sensations. In schizophrenia, the catatonic and paranoid types seem to respond better than the hebephrenic and simplex. Apathy, lack of affect, emotional blunting and paucity of delusional productivity are generally unfavorable indications prognostically, in contrast to tension, overactivity, storminess and richness of delusional material.

It is hardly necessary to remark that organic deterioration of the brain, as in cerebral arteriosclerosis and senile degenerative processes, is a contraindication to leukotomy.

The usual postoperative and convalescent complications in the eventually successful cases are confusion, restlessness, epileptiform convulsions, urinary frequency and incontinence. On the average these clear away within a few weeks to less than a year. The operative mortality is generally reported as being less than 3 per cent.

Social re-education, in the directions of guidance and support, are emphasized by Frank⁷ and by Berliner et al.⁸ as being of critical importance for the postoperative patient. Berliner and his associates regard re-education as especially valuable for patients who have been out of contact with reality for long periods, in whom every effort should be made to prevent a renewal of schizophrenic habits, early discharge is advised only if home conditions are particularly favorable. Frank is not referring only to the schizophrenic invalid in the following statement:

In psychotics who have nobody to look after them outside the hospital or whose families during the many years of illness have lost interest and sympathy for them, or whose environmental circumstances are decidedly unfavourable emotionally or materially, leukotomy is of questionable value. If one neglects the above-mentioned factors, apparently good clinical recoveries will, in the end, be disappointing.

What is considered a successful case? What is meant by "social recovery," "much improved" and "improved"? In general, authors classify patients as socially recovered or much improved if they are able to leave the hospital and to approach at least,

MEDICAL PROGRESS

PSYCHIATRY

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THE subject of psychiatry is discussed under the headings of leukotomy, shock therapy, neuro-psychiatric disorders in veterans and psychiatric education

LEUKOTOMY

During the past ten years surgical operations have been done on the frontal areas of the human brain in an attempt to relieve psychotic patients, as well as some patients with neurotic reactions, from symptoms that apparently were to be persistent and had not yielded to less drastic forms of treatment

Egas Moniz,¹ in Portugal, was the first surgeon to undertake the operation that is now known as "pre-frontal lobotomy," or "leukotomy," a better term in use in England. Moniz published his first results in 1936. Subsequently, Freeman and Watts^{2,3} developed the procedure in the United States. Briefly, the technical purpose of the operation is to cut the white matter of the frontal regions from its connections with the thalamus — that is, to perform a section of the thalamofrontal pathway. Burr holes are made in both sides of the skull, at a point 3 cm posterior to the lateral rim of the orbit (anterior margin) and 6 cm above the zygomatic process. Through the burr holes a leukotome is introduced, and section of the frontal white matter in both hemispheres is accomplished with this instrument. The cortex is not cut except in a small area for the introduction of the leukotome. The operation is done in the plane of the coronal suture. The technic has been described in detail by Freeman and Watts.³

Why patients benefit at all and to the extent that they do from this heroic operation is still basically a subject for speculation and for further neuro-anatomic and neurophysiologic research. Freeman and Watts³ state

the frontal lobes subserve the functions of foresight and insight, particularly as related to the self. It is in relation to these ego functions that the effective coloring supplied by the thalamus is of overwhelming importance for the adjustment of the individual in his social milieu.

Their theories are given special consideration in a recent monograph⁴ Cobb,⁵ who questions the assumption that the frontal areas of the brain are alone the centers for insight and foresight, presents evidence that leukotomy reduces only quantitatively the neural mechanism for the associative functions.

Whatever the reasons, if the operation is successful, the emotional intensity and coloring of the ideas,

hallucinations or somatic sensations that have plagued the patient subside to an innocuous level, and in some cases the symptoms themselves eventually disappear entirely. In other words, the effect of a successful leukotomy is to take the emotional wind out of the sails of the psychotic process. Severing the thalamofrontal radiations seems to do this. Although the operation is standardized in certain respects, the desired clinical result may depend, in the individual case, on whether the plane of section is precisely in line with the coronal suture or a number of millimeters posterior to it. In this regard, Freeman and Watts³ write as follows:

hypochondriasis and fixation of visceral complaints in involutional depressions have been satisfactorily overcome by a standard operative procedure, but a severe obsessive compulsive neurosis of long duration may require incisions from 5 to 7 mm posterior to the plane of the coronal suture. Long-standing schizophrenia requires the maximum operation. In such cases we usually operate from above, through burr holes 10 to 15 mm behind the coronal suture and 4 cm from the midline.

Another, and most important, point is that the more posterior the plane of section, the less likely it is that the patient will be able to make an even partially adequate social readaptation. Freeman and Watts³ state

in order to obtain satisfactory results sufficient fibers must be severed in order to reduce the emotional component of the psychosis to the point where the ideas no longer dominate the behavior of the patient, yet the incisions must leave sufficient quantities of the frontal lobes in order to permit the patient to make a satisfactory adaptation in a social environment. Every millimeter that the incisions trespass upon the area posterior to the plane of the coronal suture renders this adaptation less complete and more difficult.

On this fundamental issue, these authors were enabled, by multiple operations, to form some opinions, and the search for the ideal plane of section was continued.

In the successful cases, unfortunately, the patient is not benefited to the point of complete cure. If he has lost, or practically lost, his psychosis, he has paid for it with more or less profound changes in his premorbid personality. Kindwall and Cleveland⁶ point out that, although happier and easier to live with, the patient is not so able or complete a person as he was before his illness. Frank⁷ summarizes the situation as follows:

The fundamental personality pattern remains unchanged after leukotomy, it has less legend only. The emotional

*Assistant psychiatrist, Massachusetts General Hospital.

five shocks to a patient almost four months pregnant and ten shocks to one who was seven months pregnant, without premature labor or apparent damage to the mother or the child. Gralnick¹⁵ speculates whether hypoglycemia from insulin treatment caused some maldevelopment in the fetus, resulting in stillbirth.

It seems clear that, to date, there has not been enough experience with this problem to allow any general conclusions. Although Bennett does not state how many pregnant women he has successfully treated, the impression given by the reports discussed above is that electric shock may be a safer therapy than insulin for psychoses during gestation.

NEUROPSYCHIATRIC DISORDERS IN VETERANS

Although insufficient time has passed to approach the perhaps impossible problem of relating military service to the development or continuation of psychiatric disorders in the veterans of World War II, there are a few suggestions that some observers were overly alarmed in predicting a high incidence of maladjustment in the men who were in military service. In a study of 10,000 veterans, said to be representative of the bulk of the Army, Burton, Eaton and McMahan¹⁷ found only 257 men, or 2.57 per cent, who warranted a neuropsychiatric diagnosis. The men had been discharged through a separation center and thus did not include soldiers who were already in hospitals for mental or physical disability. The ages ranged from twenty to thirty-five years. Most of them had been in combat or had been overseas and had had three or more years of service. In what percentage and to what extent, since separation, these men have or will become maladjusted, of course, could not be answered by the authors.

One of their impressions is that the Army Medical Corps has done well in establishing a friendly attitude on the part of the soldier toward psychiatry. "These men no longer feel that only a 'psycho' sees the psychiatrist. From the experience gained here where several hundred thousands of men have been seen, there is no doubt that the psychiatrist has been accepted whole-heartedly." (I trust that this is so and that there can be no substantiation to the passing thought that men about to return to civilian life may well be exuberantly cordial to anybody.)

It has been remarked again and again that difficulty in adaptation to military life does not indicate an inherent incapacity for adjustment to the conditions of a more usual social pattern. In a follow-up study of 6000 men discharged from the Army in 1943 for psychoneurosis, Brill, Tate and Menninger¹⁸ estimated that 86 per cent were working full or part time. Of these men, 75 per cent had seen physicians one or more times since discharge, and

at the time of induction 51 per cent of them had considered their health none too good.

To date, according to most reports in the psychiatric literature, the person of average good integration has withstood the trials and shocks of military service without resultant chronic invalidism from psychiatric causes, and there is no convincing proof that human adaptability is on the wane.

PSYCHIATRIC EDUCATION

Psychiatry is not properly taught in most medical schools, including the best. Through generations of medical students the subject has been considered a questionable branch of medicine, if it was considered long enough to give it even that classification. It certainly did not usually attract anyone except "screw balls," and probably the men who taught it were a little on the "screwball" side. The recent war has changed this estimation to some extent, on the part not only of medical students but also of the public generally. Even before the war psychiatry was considered, in some quarters, with a little less disdain. For some years it has been so interestingly presented at University of Colorado School of Medicine that students have spontaneously taken the elective courses. With the progress of the war, the large number of men rejected from service for neuropsychiatric disability and the considerable incidence of psychiatric disorders among both men in training and men in combat areas drew, as never before, the attention of the medical profession and the public to psychiatry. Many physicians who were not psychiatrists during their service with the armed forces were brought face to face more arrestingly and convincingly than ever in civilian practice with the reality of psychogenic factors in physical disability and symptom formation.

In consequence of this sharper focus and in anticipation of an admitted need or demand on the part of many veterans for psychiatric treatment, a group of prominent psychiatrists, internists and medical educators were brought together in Hershey, Pennsylvania, in February, 1945, by the National Committee for Mental Hygiene and the Commonwealth Fund. A summary of the discussions and the recommendations of this meeting are interestingly presented in a pamphlet.¹⁹

One of the recommendations, in part, was that physicians engaged in the practice of general medicine need education on the neuroses and their care and that an experimental course, or courses, at the postgraduate level should therefore be set up promptly to develop content and methods for such education, the need for a nationwide program, in the light of such experiments, was expressed. A beginning has been made in carrying out this recommendation. For two weeks in April, 1946, twenty-five physicians attended a postgraduate course called

their former social and occupational levels. A full social recovery indicates that, after varying periods of surveillance at home, the patients conduct themselves independently, manage their own affairs and carry on with useful work in a manner that is either comparable with former standards or not necessarily equal to them. Insight into the illness is not included. "Improved" means that the patient may or may not have left the hospital, may do some simple work and is generally much less of a nursing problem than before operation.

In Frank's⁷ series of 200 cases, 84 (42 per cent) were considered social recoveries, and 57 (29 per cent) improved. The types of illness comprised schizophrenia, paraphrenia, paranoia, cyclothymia, involutional depression and chronic obsessional neurosis. The average time of observation, following operation, was fifteen months, and the range was nine months to three years. In the 100 cases reported by Hofstatter et al.,⁹ of 66 schizophrenic patients, 18 were much improved, 24 improved and 20 slightly improved, of 16 manic-depressive patients, 9 were much improved, 4 improved and 3 slightly improved, of 6 psychoneurotic patients, 5 were much improved, and 1 improved. All the patients were studied carefully for at least one year, 37 for more than two years, and 10 for more than three years. Freeman and Watts,¹¹ in a report on 50 schizophrenic patients followed for two to seven years after leukotomy, observed the following results: employed, 16 patients, keeping house, 4, studying or employed part time, 6, at home, 15, and in institutions, 9.

Over-all statistics generally indicate that at least some degree of improvement is the result, for the period of observation, in well over 50 per cent of cases after leukotomy.

From this brief outline of the procedure and application of leukotomy, it is obvious that the operation is one of amelioration, not cure. It should be, and supposedly is, limited to certain patients who are, on the whole, wrecks of human nature. With the patient who is apparently constitutionally subject to manic-depressive reactions of great sweep and intensity, the operation should not be performed until it is as certainly established as possible that periods of remission can no longer be expected. With the adolescent or young person who develops what appears to be a schizophrenic psychosis, the operation should not be done hastily, as though to save him from inevitable deterioration, since there is good evidence that some persons pass through, in biologic development, a span that seems to have the earmarks of a devastating process. On the other hand, although leukotomy is but a few years old, it seems to be the step by which some chronic mental invalids may attain contentment and freedom from harassment that otherwise they could not have.

SHOCK THERAPY

As is well known, insulin coma and electric shock do not provide a permanent cure for psychoses. The value of electric shock in terminating psychotic episodes in the affective disorders, however, is well established. Also, in some forms of schizophrenia, there is evidence that insulin treatment may effect remissions that might not otherwise occur or bring them about sooner and thus shorten the period of hospitalization.

Electric shock is far less effective in schizophrenia than it is in involutional depression and in both the manic and depressed phases of the manic-depressive psychosis. Yet its successful use is reported in acute excitement and catatonia.^{12, 13}

In spite of the most gratifying and striking results in many cases of depression, it is still to be proved that an indefinite number of electric shocks produce no permanent damage to the brain. Bennett¹² states that although there is no conclusive evidence of permanent brain damage, the total number of shocks that may safely be given is not clear. So far as the partial memory defect that, more frequently than not, accompanies a series of shock treatments is concerned, Lewis¹⁴ remarks that some patients do not regain their complete memory after many months and asks if it is possible that some never attain their original faculty.

There are no published data, so far as I know, on the correlation between the permissible number of electric-shock treatments and the probability of a lasting memory defect. It seems that such data could never be accurately collected, since there is a wide variation in original, individual memory capacity. In any event the suffering to be endured by the deeply depressed patient and the danger of suicide, as well as the social, domestic and economic ramifications, justify an initial series of five to fifteen treatments.

An interesting and sometimes important consideration is the development of mental illness during pregnancy. If, for some reason, therapeutic abortion is excluded, should shock therapy be tried? There are few reports in the literature on this question. Gralnick¹⁵ reports 2 cases, in 1 of which a thirty-two-year-old woman was given insulin-coma treatment during the second and third months of pregnancy, she apparently recovered from the illness before term but delivered a macerated fetus. The other patient, who was thirty-one years old, was given both insulin and electric shock, between the first and fifth months of pregnancy, with no improvement, and also gave birth to a macerated fetus.

On the other hand, Bennett¹⁶ reports the successful treatment, with electric shock, of a number of women in all stages of pregnancy up to within two weeks of delivery, without incident to the pregnancy. He cites an article by Polatin and Hoch, who gave

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 33091

PRESENTATION OF CASE

A fifty-three-year-old retired general entered the hospital because of intermittent pain in the abdomen and back.

The patient was known to have had hypertension for seven years and had recently been following a "rice and fruit" diet. Six months before entry he began having episodes of "indigestion," with epigastric pain and gaseous discomfort sometimes accompanied by vomiting of recently eaten food. Usually, these episodes, which numbered five in all, followed meals that had exceeded the dietary restrictions. He then remained well until five and a half weeks before entry, when he suddenly began to have sharp pain in the lower chest radiating from "the pit of the stomach" down to the toes and "stiffening" him out. For about forty-five minutes the legs were paralyzed. He was unable to move his toes, turn his feet or bend his knees, but he could roll his hips. The pain persisted until a hypodermic injection relieved him two hours later. By that time the "paralysis" had completely disappeared. During that episode the patient was nauseated and vomited several times. For the next two weeks he continued to have pains in the lower abdomen, occasionally radiating to the epigastrium. He also ran a low-grade fever and developed a stubborn constipation, relieved only by enema. The patient's wife thought that he was slightly jaundiced for a while and that his bowel movements were lighter than usual but that they quickly returned to normal. The pain gradually receded, and the patient felt better again. Two weeks before entry he developed a "twisting" pain between the shoulder blades when he assumed certain positions. Five days later x-ray examination of the chest revealed a left pleural effusion and "congestion of the lungs." At that time 350 cc of bloody pleural fluid was removed. Seven days before entry a Graham test showed nonfilling of the gall bladder, there were no stones. Another thoracentesis yielded 400 cc of similar fluid. In the interval between the two thoracenteses the patient had developed pain in the left side of the chest and also had a slight non-productive cough.

The patient denied having had any chronic cough, dyspnea, orthopnea or hemoptysis.

Physical examination revealed a well developed man in no distress. Over the entire lower left side of the chest there were diminished breath sounds, diminished tactile and vocal fremitus and dullness. Over the left thoracic paravertebral area there was a loud, rushing bruit synchronous with the peripheral pulse. The heart was normal. There was some pain at the site of an old appendectomy scar in the right lower quadrant. Otherwise, the abdomen was negative. The left knee jerk was not obtained, the right was normal. One observer thought that the pulse in the left dorsalis pedis artery was less than that in the right. The femoral and posterior tibial pulses were equal.

The temperature was 98.8°F, the pulse 85, and the respirations 20. The blood pressure was 170 systolic, 100 diastolic.

Examination of the blood disclosed a hemoglobin of 12.2 gm and a white-cell count of 10,700, with 76 per cent neutrophils and 6 per cent eosinophils. The serum protein was 6.2 gm per 100 cc. The van den Bergh test was normal. The prothrombin time was 19 seconds (normal, 14 seconds). A blood Hinton test was negative. The urine was normal. An electrocardiogram revealed a normal rhythm at a rate of 80 and a PR interval of 0.18 second. The T waves were inverted in Lead I and low in Lead 2, with a sagging ST segment, and upright in Lead 3. The chest leads showed an upright T wave in Lead CF₁, a flat T wave in Lead CF₂, and an inverted T wave in Lead CF₃. There was a slight left-axis deviation.

X-ray examination of the chest revealed a rounded mass about 8 cm in diameter lying in the left superior mediastinum somewhat posteriorly (Fig. 1). The mass could not be distinguished from the aorta. There was no definite displacement of the mediastinum or esophagus, but the mass compressed the trachea. A considerable amount of fluid was present in the left pleural cavity, particularly along the mediastinum and posteriorly. The right lung field was clear. The heart was at the upper limits of normal, but its exact size could not be definitely determined. Both leaves of the diaphragm moved equally.

During the second night in the hospital the patient had another attack of epigastric pain, severe enough to require Demerol sedation. This episode was not accompanied by vomiting. On the next morning the abdomen was soft, and no masses were felt. There was some residual tenderness in the epigastrium. The bowel movements had become normal without the use of laxatives. On the eighth hospital day a thoracentesis was performed in the eighth interspace in the posterior axillary line, and 1000 cc of clear, yellow fluid was withdrawn. X-ray examination of the chest repeated after this procedure showed a shadow through the previously noted mass.

"Psychotherapy in General Practice" at the University of Minnesota. The course was arranged by the Commonwealth Fund and the Division of Postgraduate Education of the university. The plans, procedure and immediate results of this undertaking have been recorded by Smith.²⁰

A reading of Smith's pamphlet gives the impression that the student doctors and the teachers considered the course a striking success. One of the former, a recent graduate of an excellent school, is quoted as calling the program "the most remarkable educational experience I have ever had." The course comprised lectures, section meetings, seminars, films, clinics and individual interviews with patients.

Since about 50 per cent of the patients who consult the general practitioner have complaints for which there is no discoverable physical or organic cause, it is deplorable that medical education is so derelict that otherwise competent physicians do not know what to do for such patients except to make them worse or to help them speciously and temporarily by such a statement as "There is nothing wrong with you" or by resorting to a "pill," the trust in which has, in large part, been engendered by the medical profession. It would be beneficial if such a course as that offered at the University of Minnesota could be given throughout the country, within availability for all physicians who need it.

One of the instructors in the Minnesota course stated that the overall purpose of the course was to sensitize doctors to emotional problems in their medical practice. The principal defects in the teaching of psychiatry and clinical medicine are that the immediate and pervasive effects of emotion are not delineated and stressed — for example, that diarrhea or palpitation may mean anxiety and not enteritis or heart disease — and that the student does not learn the profound importance of giving the patient enough time to talk to the point, at least, of assurance that the physician is interested in him as a human being or, in other words, that the doctor listens with genuine, not feigned, interest.

Psychiatry is not limited to the care and treatment of the psychoses. Of equal importance are the study and treatment of personality problems and the consequent emotional reactions. Therapy is most successful when it is in the hands of a physician who is sincerely interested in his patients and who gives the patients enough time and intelligent attention to work out the problems if they are possible of solution.

REFERENCES

1. Moniz, E. Les possibilités de la chirurgie dans le traitement de certaines psychoses. *Lusboa med* 13 141, 1936.
2. Watts, J. W. and Freeman, W. Surgical aspects of prefrontal lobotomy. *J Internat Coll Surgeons* 5 233 240 1942.
3. Freeman, W., and Watts, J. W. Prefrontal lobotomy: survey of 331 cases. *Am J M Sc* 211 1 8 1946.
4. *Idem*. Psychosurgery. Intelligence, emotion and social behavior following prefrontal lobotomy for mental disorders. 337 pp. Springfield, Illinois: Charles C Thomas, 1942.
5. Cobb, S. *Borderlands of Psychiatry*. 166 pp. Cambridge Massachusetts: Harvard University Press, 1943.
6. Kindwall, J. A., and Cleveland, D. Prefrontal lobotomy: fifteen patients before and after operation. *Am J Psychiat* 101 749-755 1945.
7. Frank, J. Clinical survey and results of 200 cases of prefrontal leucotomy. *J Ment Sc* 92 497-508 1946.
8. Berliner, F., Beveridge, R. L., Mayer Gross, W., and Moore, J. N. P. Prefrontal leucotomy: report on 100 cases. *Lancet* 2 325 328, 1945.
9. Hofstatter, L., Busch, A. K., Clancy, J. F., and Smolik, E. A. Results of surgical treatment in one hundred cases of chronic mental illness. *South M J* 38 604-607, 1945.
10. Halstead, W. C., Carmichael, H. T., and Bucy, P. C. Prefrontal lobotomy: preliminary appraisal of behavioral results. *Am J Psychiat* 103 217-228 1946.
11. Freeman, W., and Watts, J. W. Prefrontal lobotomy: problem of schizophrenia. *Am J Psychiat* 101 739 748, 1945.
12. Bennett, A. E. Evaluation of "shock" therapies. *Psychiatric Quart.* 19 465-477, 1945.
13. Gralnick, A. Three year survey of electroshock therapy: report on 276 cases: comparative value of insulin-coma therapy. *Am J Psychiat* 102 583 593 1946.
14. Lewis, N. D. C. Shock therapy of psychoses: evidences for and against damage. *Digest Neurol & Psychiat. Inst of Living* 13 159-169, 1945.
15. Gralnick, A. Shock therapy in psychoses complicated by pregnancy: report of two cases. *Am J Psychiat* 102 780-782, 1946.
16. Bennett, A. E. Shock therapy. *Progress in Neurology and Psychiatry*. New York: Grune and Stratton, 1946. Pp 625-648.
17. Burton, I. F., Eaton, M. T., Jr., and McMahan, H. G. Incidence of neuropsychiatric disease in demobilized veteran: study of 10,000 Army separations. *Am J Psychiat* 103 165 171 1946.
18. Brill, N. Q., Tate, M. C., and Menninger, W. C. Enlisted men discharged from Army because of psychoneuroses: follow up study. *J A M A* 128 633-637, 1945.
19. National Committee for Mental Hygiene. *Medicine and the Neurologist: Report of the Hershey conference on psychiatric rehabilitation*. 36 pp. New York, 1945.
20. Smith, G. *Psychotherapy in General Medicine: Report of an experimental postgraduate course*. 38 pp. New York: Commonwealth Fund, 1946.

DR BLAND If Dr Bauer does not ask me about the bloody fluid in the chest, I should like to ask him what sort of mass in the chest other than dissecting aneurysm involves the aorta and gives a sudden pain in the pit of the stomach, radiating down to both toes, with partial paralysis

DR BAUER On the way to this conference I asked Dr Bland if a syphilitic aneurysm ever dissected, and he said, "Yes, Dr Soma Weiss* reported three such cases" If such an event had taken place it could account for the initial attack of pain I must admit that when I read the record over last night I thought that this man had a dissecting aneurysm and my reason for retracting this diagnosis is largely on the basis of size On the other hand, I did not realize that a dissecting aneurysm could leak as it supposedly did during the first attack and not be fatal This may be the first example, of course

DR BLAND I am afraid that Dr Bauer misunderstood me The cases Dr Weiss demonstrated and reported had two processes in the same aorta syphilis and media necrosis The latter—not the syphilitic aortitis—was the cause of the dissection That might be the explanation of the onset of pain, radiating down the legs, and the partial paralysis

DR BAUER I wonder whether it was actual paralysis or inability to move the legs because of pain

DR CASTLEMAN Will you tell us what you know about this patient, Dr Leech?

DR CLIFTON B LEECH (Providence, Rhode Island) I was responsible for this patient before he entered the hospital I should be much happier about appearing here if my self-esteem were at a higher ebb than it is right now on account of the dimness of my perception in this case But I am not here to make excuses for my failure, but to give a few reasons that contributed to that failure

I had been responsible for this man since 1940, when fluoroscopy disclosed none of the abnormalities seen in the present x-ray films The impression that I got from the patient during his recent acute attack was rather different from what appears in the abstract I did not see him at 2 o'clock in the morning, when he had the sudden attack, because a nearby physician was called in to give a hypodermic injection, but I did see him at 10 o'clock that morning He did not appear seriously ill The pain was not in the chest entirely, it was largely abdominal, with some chest pain, as in the few attacks that he had had in the previous few months and that had cleared up within a few hours This pain persisted Regarding the paralysis in the leg, he mentioned that for a little while he could not move the left leg He said, "My left leg was paralyzed" I did not find anything the matter with the leg, and paid no particular attention to it The patient went on for several days with no com-

plaint aside from the pain, which was chiefly epigastric and more or less generalized He could not move his bowels although he had the urge The first of several enemas produced a little feces but after that none At the end of five days I called a surgical consultant I believed that the patient had a partial intestinal obstruction or partial ileus The surgeon had no doubt about the diagnosis of acute

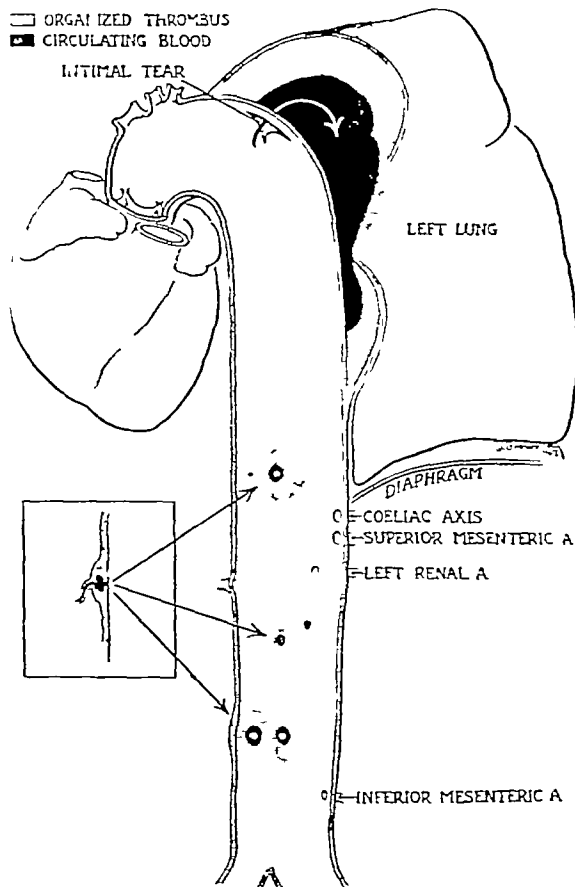


FIGURE 2

cholecystitis, which I accepted The patient continued for a week with the same symptoms At no time did he complain of discomfort in the chest The blood pressure during the periods of pain had risen to unprecedented heights for him—216 systolic, 160 diastolic I took it two or three times when he did not have pain, and perhaps as a result of morphine, it was down to 180 systolic, 100 diastolic I thought that this was a peculiar course for acute cholecystitis and asked the surgeon to see the patient again He saw no reason to change the diagnosis and postponed surgical treatment until the patient was well enough to have x-ray studies of the gall bladder At that time I am sure that the patient had no fluid in the chest

During the x-ray study of the gall bladder, the roentgenologist stated that there was fluid through-

*Weiss S Clinical course of spontaneous dissecting aneurysm of aorta. *M Clin North America* 18 1117 1141 1935

This mass was interpreted as being the descending aorta or fluid in the medial portion of the pleural cavity. There was no definite erosion or destruction of bone. Following the pleural tap, the patient had a mild chest pain for several days. On the sixteenth hospital day, he began to complain of a sense of substernal pressure and small "stabbing pains" in the chest. Another chest film on the nineteenth hospital day showed little change except possibly a slight decrease in the amount of pleural fluid.

On the twentieth hospital day just after lunch the patient coughed up a small amount of bright-red

must one assume the presence of coronary heart disease?

DR. EDWARD F. BLAND: The changes were consistent with hypertension.

DR. BAUER: May I have some help on the x-ray films, Dr. Schatzki?

DR. RICHARD SCHATZKI: I think that everything is described in the record. Something was said about a shadow that showed through the mass.

DR. BAUER: Yes, following the aspiration of 1000 cc of fluid.

DR. SCHATZKI: The word "mass" was used in the sense of something that occupies space.

DR. BAUER: I did not understand the statement.

DR. SCHATZKI: This is the mass mentioned in the record. I do not see another shadow in that region.

DR. BAUER: Is it compatible with an aneurysm of the aorta?

DR. SCHATZKI: Yes.

DR. BAUER: Were there any pulsations during fluoroscopy?

DR. SCHATZKI: I do not believe so.

DR. BAUER: I must admit that when I first read the history my immediate reaction was that this patient had an aortic dissecting aneurysm. As I read on, however, I wondered whether all the findings could be explained satisfactorily on this basis. I did not believe that any type of mediastinal tumor, benign or malignant, could account for the sequence of events as recorded. I wondered somewhat about the possibility of a mediastinal abscess, but again there seemed little to justify or lend support to such an interpretation. Prior to seeing the x-ray films, I considered syphilitic aneurysm or a dissecting aneurysm of the aorta as the likeliest diagnostic possibility. From the record alone I was inclined to favor an aneurysm that had first dissected downward and subsequently upward. I must admit, however, that I found it difficult to account for the pleural effusion. I was not aware of the fact that a dissecting aneurysm could leak without being fatal. Having seen the x-ray films, I favor the diagnosis of an aortic aneurysm. I assume that it leaked for a time five and a half weeks prior to entry and finally ruptured, causing death. I am not certain that this diagnosis explains all the findings — for example, the two aspirations of bloody pleural fluid and a third that was yellow. There are a few other discrepancies. In favor of syphilitic aneurysm, however, were the x-ray findings, the bruit and the absent knee jerk on the left. True enough, the blood Hinton reaction was negative. The evidence in favor of syphilis is as complete as one might like.

DR. BENJAMIN CASTLEMAN: Do you believe that this was a saccular aneurysm rather than a dissecting one?

DR. BAUER: Yes, I do not believe that a dissecting aneurysm ever reaches this size, but I may be expressing my ignorance of dissecting aneurysm.



FIGURE 1

blood (enough to stain six Kleenex tissues). He had no pain. The physical findings at that time were unchanged except for a moderately loud apical systolic murmur that had not been heard previously. Fifteen minutes later the patient complained of a sudden, severe, crushing pain in the left side of the chest. He rapidly became white, clammy and restless. The blood pressure fell to 60 systolic, 40 diastolic. The breath sounds were diminished over the entire left side of the chest, and there was dullness in the posterior axilla. He was placed on shock blocks and given oxygen by Boothby mask, as well as 1000 cc of whole blood. The blood pressure returned to 130 systolic, 80 diastolic, and his condition remained satisfactory for twelve hours. On the following morning he again coughed up a small amount of bright-red blood and complained of severe pain in the center of the chest and of inability to breathe. He became restless, pale and sweating and died within thirty minutes.

DIFFERENTIAL DIAGNOSIS

DR. WALTER BAUER: Could the electrocardiographic changes have been due to hypertension? Or

mouth floor and elevating the tongue. There was an area of anesthesia, about 3.5 cm in diameter, at the angle of the mouth on the right.

The routine admission laboratory findings were normal. The blood calcium was 9.2 mg, and the phosphorus 4.2 mg per 100 cc, and the phosphatase 40 Bodansky units.

An x-ray film taken in the Tumor Clinic just before admission revealed a large soft-tissue mass arising from the chin and protruding slightly to the left side (Fig. 2). The anterior aspect of the jaw on both sides, as well as in the region of the chin, showed extensive bone destruction involving the lower two thirds of the jaw. The destructive process had caused the isolation of several bone fragments. No calcification was seen in the soft-tissue mass, and no evidence of periosteal activity was present. An x-ray film of the mandible and of the upper cervical spine taken two days after admission revealed bone destruction as far as the second molar area, with involvement of several teeth.

On the fourth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR HENRY M. GOLDMAN: As can be seen from a photograph of this girl, the tumor had grown to a considerable size before admission.

The history states that the patient had a painless mass poorly attached to the jawbone on the right side. The fact that the mass was poorly attached



FIGURE 1

to the jawbone suggested to her physician that it was an inflammatory "gland," and he gave her some pills. The mass did not regress, however, and on an attempt to drain it, only blood was recovered. One can assume that a tumor already existed and that the "gland" was a part of the lesion. The fact that the patient had pain around the teeth a month later seems to denote that the tumor had invaded the body of the mandible and had involved the periapical region of one or more teeth. This tooth or those teeth were probably loose, a finding that is often the first evidence of a malignant lesion of the jaw. The x-ray film taken at that time was described as "not remarkable." I highly question this because

there must have been some change, since a film taken ten days later showed extensive destruction of the mandible. This brings up two possibilities: in the first place, the tumor may have invaded along the mandibular canal, causing extensive destruction in a short time, and secondly, extensive invasion may have taken place because of a highly malignant tumor. The patient developed numbness of



FIGURE 2

the right chin and the lower lip, which reinforces the suspicion that the tumor had invaded the mandibular canal and had involved the inferior mandibular nerve.

Reviewing the history up to this point, I believe that the tumor was originally periosteal or endosteal and later extended peripherally and internally.

The blood studies were negative and rule out any of the skeletal diseases.

X-ray examination showed an osteolytic process involving the middle portion of the mandible and appearing as spotty irregular radiolucent areas. A large, soft-tissue mass was seen extending from the jaw, no calcification was observed in the soft tissues and no periosteal activity was present.

In summarizing the history, one can say that this was not an inflammatory lesion. This rules out an osteomyelitis or anything of that nature. We know that this was a rapidly growing, invasive tumor and therefore a highly malignant one.

The first thing to think of is an osteolytic osteogenic sarcoma, with which the patient's age and the roentgenologic evidence are consistent, and on the law of chance that is a reasonable diagnosis to make.

out the chest. The signs of fluid were unmistakable. I had questioned the patient closely about chest symptoms, and he said that he had a little pain between the shoulder blades if he moved in a certain way. Paracentesis yielded 350 cc of uniformly bloody, almost ruby-red fluid. My thought was that in addition to the hypertension and acute cholecystitis he had a mediastinal tumor with pleural involvement, and I had no hesitancy in allowing him to go back to the roentgenologist's office for completion of the studies, which were reported to me as showing a large left superior mediastinal mass, with pleural fluid, and a nonfunctioning gall bladder.

Two days after the first chest tap I again removed 400 cc of uniformly bloody fluid. For the first time the patient admitted discomfort in the area of the tap. I accepted the roentgenologist's diagnosis and made arrangements for him to come up to see Dr. Churchill. Although the record does not so state, he had a third attack two days before he came here. He also had a small amount of bloody fluid at that time.

A PHYSICIAN: Was he jaundiced at that time?

DR. LEECH: No.

DR. BAUER: I should like to go back to my first diagnosis — a dissecting aneurysm of the aorta.

CLINICAL DIAGNOSIS

Dissecting aortic aneurysm, with rupture.

DR. BAUER'S DIAGNOSIS

Dissecting aneurysm of aorta, with rupture.

ANATOMICAL DIAGNOSIS

Dissecting aneurysm of aorta, with rupture into left pleural cavity and with localized expansion and partial healing.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At autopsy the left pleural cavity contained almost 3000 cc of blood. The source of this blood was a ruptured aortic dissecting aneurysm (Fig. 2). The intimal tear was located just beyond the arch, at the beginning of the descending thoracic portion. It was a triangular tear leading into a large sac, 8 cm in diameter, that was lined with partially organized clot and filled with fresh blood. This sac was really a greatly expanded portion of the dissecting aneurysm, or what might be termed a medial hematoma, because it is within the media that dissection always occurs. It produced the large mediastinal shadow observed on x-ray examination. Farther down the aorta we found another similar but smaller medial expansion that was almost completely filled with organized clot and a little fresh blood. These two sacs were connected. Following the aorta down still farther we found dissection as far as the iliac arteries. This portion of the dissection, however, was organized, measuring at the most 1 mm in width. A similar healed dissection extended

proximally from the intimal tear down to the aortic valve. It did not appear to involve the coronary mouths. There was evidence of some dissection around the mouth of the right renal artery and especially around several of the lower intercostal arteries, where there were localized expansions within the aortic wall measuring up to 1 cm in diameter. These were undoubtedly the cause of the transient leg paralysis, since the intercostal arteries supply branches to the spinal cord.

I believe that the sequence of events was as follows. The intimal tear and dissection occurred five and a half weeks before entry. Most of the blood in the aneurysm organized, leading to obliteration of the channel, except in the region of the intimal tear, where the localized medial hematoma increased gradually in size until the pressure was so great that the external wall gave way. There probably was a slow oozing of blood through this sac, which would account for the hemorrhagic pleural fluid removed by Dr. Leech two or three times. If clear fluid was obtained, I believe that the blood had settled and that this was supernatant fluid above the blood clot.

A PHYSICIAN: Why did the patient have a hemoptysis?

DR. CASTLEMAN: The aneurysm was adherent to the left upper lobe, and there was a little oozing of blood into the lung parenchyma.

There was no evidence of syphilis. This was a case of media necrosis aortica cystica. We have had one other case of aortic dissection with a large medial hematoma such as this.

CASE 33092

PRESENTATION OF CASE

A seventeen-year-old unmarried salesgirl was admitted to the hospital because of a painless mass in the jaw.

About three months before entry the patient noted a hard 2-cm mass, which seemed poorly attached to the jawbone on the right. A physician thought that it was a "gland" and gave her pills. When it did not regress he attempted incision and drainage but obtained only blood. About a month later, when the left lower incisor teeth began to ache, the patient was referred to a dentist for x-ray studies. Three weeks later the swelling had enlarged, the right jaw had begun to ache, but an x-ray film was not remarkable. A repeat x-ray examination ten days later revealed extreme destruction originating within the right side of the mandible and extending to include the symphysis. A week before entry numbness developed in the right chin and lower lip.

Physical examination revealed a symmetrically enlarged, hard, insensitive mass about the size of a pear jutting from the chin (Fig. 1). It was continuous with the mandible and lay immediately beneath the dusky tense skin, presenting inside the

nant, and the prognosis is poor. Some that I have seen have invaded the bone, and others have not. In one case, spicules of bone extended into the tumor, as seen in osteogenic sarcoma. These spicules are generally metaplastic bone growing from the jaw into the tumor. The third is the central type of sarcoma, which develops most frequently in the mandibular canal, from connective tissue around the nerves or blood vessels, with consequent pain, paresthesia, numbness of the lip, and loose teeth. Finally, the tumor generally is visible inside as well as outside the mouth, changing the appearance of the face. I believe that this tumor originated from the periosteum and invaded the jaw secondarily.

DR GRANTLEY W TAYLOR: We went through much the same process of reasoning as Dr Goldman. In the Tumor Clinic, our first effort was to get an accurate diagnosis of the histologic type, because if the tumor was sensitive to radiation, we thought that that might be the proper way to handle it. Operation seemed almost impossible because of the extension of the tumor far back in the floor of the mouth, but following biopsy, which intimated to us that the tumor would be unlikely to respond favorably to radiation therapy, we decided on radical operation. We were able to remove the entire tumor, apparently without leaving any local process behind. We took some encouragement from the fact that before operation there was no evidence of dispersion or dissemination of the tumor. As Dr Thoma pointed out, fibrosarcomas in relation to the mandible behave differently in general from those elsewhere in the body, may be confined as a local process longer and are less likely to disseminate. We therefore have some hope that this girl may have been cured by the mutilating operation. If so, she has her whole life before her, and the problem of restoration of function can be carried out at leisure.

CLINICAL DIAGNOSIS

Sarcoma of jaw

DR GOLDMAN'S DIAGNOSIS

Periosteal fibrosarcoma of jaw

ANATOMICAL DIAGNOSIS

Periosteal fibrosarcoma of jaw

PATHOLOGICAL DISCUSSION

DR MALLORY: On the biopsy we reported osteogenic sarcoma. With further study I have changed my mind.

The photograph of the resected specimen (Fig 3) shows that nearly all the mandible was resected. The bulk of the tumor was extraosseous, but there was tumor growth within the mandible itself. The sections disclosed a spindle-cell tumor that was rapidly growing, evidently highly malignant and rather poorly differentiated. In one of eight sections two small spicules of osteoid were found. Some question arises whether on that basis it was fair to consider this an osteogenic sarcoma. My opinion is that that diagnosis was not correct, that these spicules represented a slight reactive periosteal bone formation, which Dr Thoma mentioned, and that the tumor must be classified as a periosteal fibrosarcoma.

DR VINCENT DOLE: Do you think that the incision done elsewhere had any influence on the spread or extension of the tumor?

DR MALLORY: I cannot answer that question. Such an incision is certainly something that all of us prefer not to have done.

A periosteal fibrosarcoma is suggested by the fact that the mass started in either the periosteum or the endosteum. The patient was in the correct age group for this tumor also. The lack of osteoblastic activity in the x-ray film makes me lean toward a fibrosarcoma. I think that a Ewing tumor should also be considered — the age is again right. The



FIGURE 3

history does not mention any injury or blow, but that is a possibility. There was no history or x-ray evidence of multiple myeloma, since this was a solitary lesion and did not run the course of myeloma, I shall dismiss that diagnosis. I also thought of a neurogenic fibrosarcoma, for which I think the possibilities are good, an angiosarcoma and finally a metastatic tumor. This could have been a metastatic tumor from a primary tumor in some other area — a kidney tumor, for instance. That is not too rare. I think that that possibility should definitely be considered.

Going through such a differential diagnosis, one comes down to a preoperative diagnosis of either osteogenic sarcoma or periosteal fibrosarcoma. I finally concluded that it was a highly malignant tumor that had probably metastasized and should have been resected immediately and that it was a periosteal fibrosarcoma.

DR JAMES R. LINGLEY: The tumor is adequately visualized in this lateral view, which shows a mass within the jaw. There is no calcification. The lesion is predominantly destructive. The only new bone

is anteriorly, with a little periosteal malformation. The process involves more of the right side than the left.

DR JOSEPH C. AUB: Do you have the x-ray film taken ten days previously?

DR TRACY B. MALLORY: They were taken in another hospital, and we were not able to get them.

DR AUB: It is hardly likely that they were normal.

DR MALLORY: We all agree on that. Do you wish to express an opinion, Dr. Sosman?

DR MERRILL C. SOSMAN: The lesion looks purely destructive. There is no obvious new-bone formation, and no reactive bone, such as one might expect with an inflammatory process. The only new bone is periosteal, anteriorly and just below the incisors. This fits in quite well with Ewing tumor. The margin of an osteogenic tumor is often raised, forming the reactive triangle described by Codman. The tumor spreads along the shaft, raising the periosteum and forming a marginal triangle until the tumor destroys the new bone. One thing not emphasized is the point of origin, which is apparently the anterior margin of the bone and not the tooth. All the roots of the teeth, so far as I can see, are normal, so that the tumor presumably did not originate from any of the dental structures per se. We can rule out the adamantinomas and the whole group associated with the embryology of the dental structures in the development of this tumor. I should interpret it as a highly malignant growth, probably osteogenic sarcoma or Ewing tumor.

DR KURT H. THOMA: It is significant that the tumor was not entirely in the bone, which is the site of an adamantinoma, although it is not entirely outside. In tumor of the jaw the main point to decide is whether it originated in the bone and grew in both directions — in the manner of a Ewing tumor or an osteogenic sarcoma — or whether it remained within the limits of the bone as do the central tumors of nonosteogenic origin, or whether it developed from the periosteum and later invaded the bone. If we can trust the former x-ray diagnosis and also the statement regarding the onset of the disease, it seems to me likely that the tumor originated from the periosteum. Therefore, it was a periosteal fibrosarcoma, which invaded the jaw.

There are three types of fibrosarcoma that occur in the jaw. One, which is intraoral, developing from the periosteum of the alveolar process or periodontal membrane, forms multiple masses and is not so malignant as the subcutaneous type. There is a series of 35 cases reported by Pollack* in 1936 in which 25 patients had lived from six months to twelve years without recurrence, 3 were unimproved after operation, 3 had recurrences in from two to eight years, and in 3 the outcome was unknown. The second type of fibrosarcoma, which develops in the subcutaneous region of the jaw, is more malig-

*Pollack, W. *Das Schicksal der malignen Tumoren aus der Westdeutschen Kieferklinik seit dem Jahre, 1920*, Düsseldorf 1936.

the school nurses and, indeed, to the teacher who is closest of all to her charges

Finally the practicing physician concerned — the family doctor or pediatrician — must be brought into the picture. Only with his interest and co-operation can a successful, fully rounded school health program be developed. On his advice a final decision often rests, and it is frequently he who must see that corrective measures are carried out.

SMALLPOX DECLINES

"SMALLPOX, once the scourge of our forefathers," wrote the late Dr. Benjamin White,* when he was director of the Massachusetts Antitoxin and Vaccine Laboratory, "has become such a rare disease in Massachusetts that we have become unmindful of its pestilential power. We do not realize that it still exists with all its horrible features, and that instead of being conquered, it is at best only held at bay by the continued practice of vaccination."

The world has always had its various pestilential visitations, coming at greater or less intervals over the centuries, and eventually sparing those countries where scientific control has been most intelligently applied. Smallpox of these, has been the most tenacious, the most persistent, the one most frequently recurring in the long history of the scourges of mankind. It is known to have existed in Asia before the Christian Era, it came to Europe as early as the sixth century, reaching its height in the seventeenth and eighteenth centuries, it invaded the New World in the wake of the earliest pioneers. Thus, in the German-speaking countries, according to White, over 65,000 persons died of smallpox in 1796, in the early nineteenth century, 40,000 people succumbed annually in Prussia, and Boston itself was visited by smallpox in epidemic form twelve times between 1649 and 1792. Admiral Berkeley, in a speech before the House of Commons in 1802, said "It is proved that in this United Kingdom alone, 45,000 persons die annually of the smallpox, but throughout the world what is it? Not a second is struck by the hand of Time but a victim is sacrificed upon the altar of that most horrible of all disorders, the smallpox."

*White B. *Smallpox and Vaccination*. Harvard Health Talks. 90 pp. Cambridge: Harvard University Press. 1924.

These words are written about a disease known since 1798 to be preventable and one against which the technic of prevention has been of late years so successful that in 1945 only 346 cases were reported in the entire United States, and only 5 in Canada. These figures, according to the Metropolitan Life Insurance Company's Information Service, represent the lowest ebb that smallpox has ever reached in the United States and, incidentally, furnish an example of what preventive medicine can accomplish, particularly when these cases are compared with 48,920 reported as recently as 1930. It is of local interest to note that the five New England states are included among the thirteen that were entirely free of the disease, and that the thirteen, although not representing exactly the original thirteen colonies, are all on the Atlantic seaboard.

It must be constantly emphasized, however, that eternal vigilance is the price paid for security that where vaccination lapses smallpox occurs. Any reservoir of infection is the potential focus of future smallpox epidemics, and the return of members of the armed forces from overseas constitutes an extra hazard. To servicemen returning from the Orient can be attributed the recent outbreaks of virulent smallpox in San Francisco and Seattle, which fortunately, were quickly brought under control by quarantine and mass vaccination.

MASSACHUSETTS MEDICAL SOCIETY COMMITTEE TO MEET WITH GENERAL HAWLEY

Members of the Massachusetts Medical Society who wish to participate in the plan for the local care of veterans and who have not yet sent in their registration forms are urged to do so at once.

Those physicians who have already registered as specialists, and who would also like to give general physical examinations should communicate with Humphrey L. McCarthy, M.D., 479 Beacon Street, Boston.

HUMPHREY L. MCCARTHY, *Chairman*

DEATH

GRANT — Justin F. Grant, M.D., of Boston, died January 26. He was in his sixty-ninth year.

Dr. Grant received his degree from Johns Hopkins University School of Medicine in 1903. From 1903 to 1910 he was professor of anatomy and pathology at the University of West Virginia and from 1910 to 1912, professor of anatomy at the Atlanta College of Physicians and Surgeons. He had practiced in Boston for many years. He was a fellow of the American Medical Association.

A sister, a son and a daughter survive.

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

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SCHOOL HEALTH SERVICES

EVERY so often, at more or less irregular intervals, we become conscious of the fact that the child is father of the man and that something ought to be done about it. There may be many causes for such awakenings, but they are sure to come after the examination of recruits in time of war — a chastening experience. They may result in another White House conference or in a nationwide study of child health services or in a determined reformulation of our school medical services.

School medical services have come much to the fore in the last few years. They have been studied by a committee of the American Academy of Pediatrics, with recommendations. *Suggested School Health Policies* has been published by the Health Education Council, and the Massachusetts Medical

Society, through a subcommittee, has investigated local conditions in the Commonwealth. The whole situation is admirably summarized elsewhere in this issue of the *Journal* by Dr. George M. Wheatley, assistant vice-president of the Metropolitan Life Insurance Company.

Four essential factors are necessary for the improvement of medical service in the schools "co-operation between education and public-health authorities, provision for health services in the school that are satisfactory learning experiences for children, properly qualified school health personnel and the development and strengthening of relations with the medical profession."

At present in many states there are heartaches over the division of responsibility for school health between departments of education and departments of health. Friction and jealousy exist where properly worked out co-operation could bring contentment to both parties and improved service to the public.

The value of the physical examination often suffers, both because of undue restrictions that have been imposed by overmodest lawmakers who have refused to allow sufficient clothes to be removed from the child and because of overspecific requirements, such as where an annual examination is established by law regardless of lack of personnel to carry it out properly.

The function of the examination as a learning experience to the pupil is lost if it is casual or hurried, with no opportunity for a real "consultation", and with younger children, corrective measures usually fail if the parent is not induced to be present. The time of the examination, if it is a good examination, has been aptly termed the "most 'teachable moment' — the best educational opportunity that exists in the schools," and the moment is often lost.

The school physician must himself be rescued from a situation where, often, as a harassed, underpaid official, untrained for the particular work in which he is engaged, he is doing poorly a part-time job for what little money there is in it. School health is a dignified, vital branch of public health, and it should be in the hands of capable, well trained, adequately paid career men and women. This applies not only to the physicians and dentists but to

CORRESPONDENCE

ILLEGIBLE AND INCOMPLETE DEATH CERTIFICATES

To the Editor Since assuming the office of City Registrar I have become increasingly aware of a condition in the writing of original certificates of death by physicians that creates a serious hardship on all who are engaged in the processing of these documents, including the personnel of the Registry Department. The certificates, in many instances, are illegibly written, the required data are lacking and there are numerous other conditions which make the copying of these records almost an impossibility without soliciting confirmation by telephone from the physician who made out the certificate or referring to medical dictionaries in an effort to determine clearly the causes of death.

It is not my purpose to become critical of the medical profession, recognizing only too well the tremendous task imposed on physicians at this time, but it is my feeling that if this matter could be brought to their attention an improvement in the quality of the records being forwarded to this department might be brought about.

City Hall Annex
Boston 8

MICHAEL J. MANNING,
City Registrar

AORTIC OCCLUSION

To the Editor. Dr. Edward D. Maire's article, "Coarctation of the Aorta," which appeared in the January 2 issue of the *Journal* was stimulating. He failed, however, to mention a condition in his paper that I believe should be called to the attention of your readers. This is atheromatous occlusion of the abdominal aorta or of both common iliac arteries.

The brachial blood pressure in many cases is elevated. The pressure in the lower limbs is invariably low. The femoral pulsations are reduced or absent. Symptoms due to the ischemia of the lower extremities, such as intermittent claudication, pain and early fatigability, are usually present. In the differential diagnosis evidence in favor of coarctation of the aorta, such as scalloping of the ribs and absence of the aortic knob, is lacking. Evidence in favor of atheromatous occlusion consists of the following: the onset of initial symptoms past middle age, the presence of x-ray findings of calcification of the aorta or iliac or femoral arteries, and the presence of diabetes or hypercholesterolemia. The abdominal aorta may also be occluded from other causes, such as an ovarian cyst. In such cases the presenting symptoms usually include the intra-abdominal mass.

Owing to the fact that there is no practical method of exploration of the abdominal aorta, its occlusion is frequently overlooked. A method of retrograde abdominal aortography has been reported by Dr. P. L. Farnas (*Surgery* 18:244, 1945, and *American Journal of Roentgenology and Radium Therapy* 55:448, 1946). I doubt, however, that this method will receive widespread use in this country.

ROY J. POPKIN, M.D.

2007 Wilshire Boulevard
Los Angeles

BOOK REVIEWS

Principles of Dynamic Psychiatry, Including an Integrative Approach to Abnormal and Clinical Psychology. By Jules H. Masserman, M.D. 8°, cloth, 322 pp., with 4 plates. Philadelphia and London: W. B. Saunders Company, 1946. \$4.00.

This is another volume of psychiatry that will not be generally adopted as a textbook for academic undergraduate teaching. The author states that his immediate purpose of getting into print is to express certain fundamentals of modern dynamic psychiatry that are now being taught by him and his colleagues only through lecture and precept. He has sought for books that, breaking with tradition, present the fundamentals of dynamic psychology and clinical psychiatry briefly, clearly and systematically. In his attempt to bring together the psychoanalytic, biologic and physiologic approaches, his formulations are not always presented briefly, clearly and systematically.

Behaviorism is rather in the foreground, illustrative clinical records are utilized freely, and original animal experiments

contribute the most intriguing part to the book. The student may be misled to believe these to be the stuff that so-called "dynamic psychiatry" is made of. "Biodynamics of Normal and Abnormal Behavior" is a long and involved chapter in which the author attempts to correlate various theories, some of which are fundamentally and traditionally opposed to each other. He admonishes man to cease thinking of himself as so different from other animals, and he states that "psychology and psychiatry may profit immeasurably by becoming more 'catomorphic' or even 'amoebamorphic' as corrective steps toward the ultimate conceptual integration of all behavior theory."

The author has put much work in this volume, which will be read with interest by specialists. He refers repeatedly to a companion volume on clinical psychiatry and therapy that is to follow.

Considerable space is given to neurotic reaction types and borderline cases. The psychoses are not the center of the work, and the author has studiously deviated from the orthodox diagnostic formulations and psychiatric clinical entities.

There is a complete bibliography and a glossary of about twelve hundred psychiatric terms that will be helpful to the student.

Modern Trends in Child Psychiatry. Edited by Nolan D. C. Lewis, M.D., and Bernard L. Pacella, M.D., with the assistance of Gertrud M. Kurth, Ph.D. 8°, cloth, 341 pp. New York: International Universities Press, 1945. \$6.00.

This volume contains the lectures on child psychiatry and guidance given at the New York State Psychiatric Institute by leading authorities in 1943 and 1944. The various aspects and manifestations of anxiety and the primary behavior disorders, psychiatric reactions and delinquencies in children are dealt with. New methods and techniques in diagnosis and therapy, as well as the psychobiologic approach, emphasizing parent-child and living social relations, are discussed. This book is valuable as a record of the lectures and should be in all psychiatric reference collections.

Bioenergetics and Growth, with Special Reference to the Efficiency Complex in Domestic Animals. By Samuel Brody, Ph.D. A publication of the Herman Frasch Foundation. 8°, cloth, 1023 pp., with illustrations and tables. New York: Reinhold Publishing Corporation, 1945. \$8.50.

This volume records investigations made in the comparative study of the energetic efficiencies of agricultural processes. The subjects discussed cover a wide territory. Many of the factors influencing efficiency, such as enzymes, minerals, vitamins and hormones, are analyzed largely with the aid of the literature on the various subjects. The material is well documented and contains much of value in comparative physiology, especially concerning homeostasis, calorimetry, metabolism, growth rates, aging, nutrition and muscular work. The text is well written and illustrated with graphs, charts and tables. It is printed with a good type on good paper. This valuable work should be in all physiologic reference collections.

Journal of the History of Medicine and Allied Sciences. Vol. 1, No. 1 (January, 1946). 4°, cloth, 182 pp. New York: Henry Schuman, 1946. \$2.50.

The publication of a new quarterly journal devoted to medical history and the allied sciences will receive a warm welcome from medical historians in America and throughout the world. With the coming to an end of the *Annals of Medical History*, the United States was left with only one journal, the excellent *Bulletin of the History of Medicine*, to supply a growing need for publications in this field. Many foreign journals, of similar scope, were discontinued during the war, some permanently.

The new journal fills a want and does it admirably. Neat in appearance, expertly edited and well printed and illustrated, this publication fully justified its existence in the first number, issued in January, 1946. Subsequently, three other numbers have more than come up to expectations set by the initial issue. The editor, Dr. George Rosen, is ably assisted by a board of qualified historians and consulting editors from many countries. No student of medical history can afford to miss a single number, and all libraries, medical as well as general, should subscribe.

A HUNDRED YEARS AGO

Letters and printed reports by the last steamer show that the Boston Letheon is well received in London. Mr. Liston, the great surgeon, has amputated twice with marked satisfaction, while the patient was under its influence. — On Wednesday last, although the weather was unfavorable, a good number of Counsellors of the Massachusetts Medical Society were punctually present at 11 o'clock, the hour designated in the notices of their meeting. Some alterations were made in the by-laws, which in due time will be published. Dr. Bigelow, the President, announced that he should not be a candidate for office the ensuing year. A change of feelings, and of policy, too, on the part of some of the gentlemen who opposed the election of delegates to the last National Medical Convention, was as striking as it was gratifying. The following members were nominated from the Chair, and elected delegates to the next National Convention in May, viz, Dr. Stephen W. Williams, Deerfield, Dr. Enoch Hale, Boston, Dr. Elisha Huntington, Lowell, Dr. A. L. Peirson, Salem, Dr. Royal Fowler, Stockbridge, Dr. J. V. C. Smith, Boston, Dr. Joseph Sargent, Worcester, Dr. Z. B. Adams, Boston, Dr. Lyman Bartlett, New Bedford, Dr. E. W. Carpenter, Sandwich, Dr. Wm. Bridgeman, Springfield, Dr. O. W. Holmes, Boston, and Dr. George C. Shattuck, Jr., Boston. Other business was despatched actively, yet with due regard to the best interests of the institution and those associated with it. — A lady, in the West, recently gave birth to four daughters, all represented to be doing well. — In the fifth Massachusetts Registration Report, several tables are presented to show the average value of life in persons who pursue different occupations. Fourteen clergymen were carried to an aggregate of 897 years, which shows the average age to have been 64.07 years. Eight lawyers lived to an average of 59, by which it appears that there is nothing essentially injurious to the machinery of organic life in that profession. Twenty-one physicians had allotted to them an average of only 47.64 years. There are few or no holidays for this class of men. Professional cares prey upon constitutions operated on by other forces, such as exposure to all the vicissitudes of weather, broken sleep, irregular meals, etc., which individually war against a long life. Teachers are on the gain in point of longevity, which may probably have been caused by the better systems of ventilation demanded from one season to another by those who are especially interested in the public health. Those styled gentlemen, in the old Puritan Bay State, seem to have spun out the thread of life to a very satisfactory period. A furnace man had the shortest life in the whole column of 137 trades and professions. It may be remarked, with safety, that there is room for vast im-

provement in this new idea, in the United States, of registration. — Dr. I. P. Smith, of Gloucester, reports the case of a woman who was married young and at the time considered a remarkably slender girl, being subject to cough upon the slightest exposure. Her only brother and sister both died of *tubercular phthisis* and both parents also died of the same disease. She was 39 years old on October 28th, 1846, and never had a sick day since her marriage December 9th, 1826, except the usual sickness consequent on parturition. During this period she has given birth to eight children all of whom are now living and in perfect health. She has been constantly nursing for a period of nearly twenty years — never weaning one child till the birth of another compelled her to, for the convenience of the infant. More than once, when in labor, Dr. Smith has seen her child of the last birth at the breast. He wishes to know whether, if similar cases with a like favorable result are reported, *protracted lactation*, especially during pregnancy, might properly be inferred to possess a prophylactic power, even when there exists a well-marked hereditary predisposition to pulmonary disease. — A public announcement has been made in New York of another new "discovery" under the name "spirometer" for ascertaining the condition of the lungs and "air passages." Physicians and the public have been lately invited to the Astor House to inspect the instrument. Those who have responded to the call have been introduced to a gasometer, resembling those seen in every chemist's laboratory and used in ordinary by the public exhibitors of the laughing gas. Its only novelty or improvement consists in a tube movably attached to the top of the gas holder, while itself is filled with water, and a scale attached to the top of the cylinder designed to show the amount of air which an individual can expire by blowing into the tube. The idea that even having ascertained the capacity of the lungs, by measuring the volume of air expelled by a full expiration, we should thereby learn anything of the true pathological state, in the variety of morbid affections of the pulmonary tissues, is a *reductio ad absurdum* in itself, besides being at war with medical philosophy and the lessons of experience. — The *Boston Transcript* intimated last week that Dr. Warren was about resigning his connection with the Medical College in this city. — At a meeting of the Committee on Dissertations of the Boylston Medical Society held February 10th, three prizes were awarded. The dissertations this year, we learn, were of an unusually high order, and some difficulty was experienced in making a selection by the Committee. — Extract from the *Boston Medical and Surgical Journal*, February, 1847.

Contributors to the various sections are all well known in their fields. The various chapters are written in a clear, common-sense manner. There should be no difficulty in following the instructions given. Although one might prefer, for the sake of completeness, to have all motor skeletal difficulties discussed, only those amenable to surgical therapy are mentioned. Most doctors with experience in orthopedic surgery will not agree unreservedly with the treatment suggested, but they will learn — as the reviewer has learned — many helpful new points in therapy. The second volume is especially well done. The format is good, and the printing and the illustrations are excellent. These helpful and practical books can be recommended and will be most useful to orthopedic and industrial surgeons.

Correction. In the listing of *A Bibliography of Infantile Paralysis*, a review of which appeared in the January 2, 1947, issue of the *Journal*, it is erroneously stated, "Compiled by Ludwig Hektoen, M.D." The statement should read, "Compiled by Ludwig Hektoen, M.D., and Ella Salmonsens."

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Electron Microscope. An introduction to its fundamental principles and application. By E. F. Burton, head of the Department of Physics and director of the McLennan Laboratory, University of Toronto, and W. H. Kohl. Second edition. 8°, cloth, 325 pp., with 125 figures and 66 plates. New York: Reinhold Publishing Corporation, 1946. \$4.00.

This second edition of a standard work has been revised throughout, and the text has been rearranged. The aim of the book is to provide an introduction to the fundamental principles and applications of the electron microscope, and in this connection some material has been eliminated as being too special for the scope of the book. The detailed description of the Johansson-Brüche electrostatic electron microscope has been omitted from this edition, and the chapter on the history of the electron microscope has been eliminated, parts of this chapter being incorporated in other chapters. The chapters on electron optics have been enlarged, and the chapter on the compound magnetic electron microscope has been rewritten completely and much new material added. In the chapter on the application of the microscope, which has been largely rewritten, the illustrations of the accomplishments of the microscope are included. A complete bibliography recently prepared by Claire Marton, of Stanford University, and Samuel Sass, of the University of Michigan, is included with the permission of the authors and the publishers. Some data have been added concerning the organization of the Electron Microscope Society of America. Both the first and second editions of this book should be in all libraries having an interest in the subject.

Public Health the American Way. By H. B. Anderson. 8°, cloth, 238 pp. New York: Citizens Medical Reference Bureau, Incorporated, 1945. \$2.50.

The central thought that this book seeks to convey is that compulsory sickness insurance and similar schemes to socialize medicine nullify the Bill of Rights of the Constitution.

Trends of Mental Disease. American Psychopathological Association. 8°, paper, 114 pp. New York: King's Crown Press, 1945. \$2.00.

This small monograph, by various authors, constitutes a statistical analysis of the incidence of mental disease. The authors discuss the census statistics of patients in hospitals for mental disease in the period 1933-1942, the expectation of mental disease in New York State during the years 1920, 1930 and 1940, and the trend of mental diseases in Illinois during the period of 1922 to 1943. Two concluding chapters

consider the trends of mental disease in the Navy and the neuropsychiatric screening of Selective Service registrants in New Jersey. The first chapter forecasts the trends of mental disease in the United States during the period 1940 to 2000.

A Blind Hog's Acorns. Fignettes of the maladies of workers. By Carey P. McCord, M.D. 8°, cloth, 311 pp., with illustrations by Strobel. Chicago: Cloud, Incorporated, 1945.

The author, who is a specialist in the field of occupational diseases, relates his experiences as an industrial physician.

1021 Answers to Industrial Health and Safety Problems. Edited by Jack C. Weiss, editor, *Occupational Hazards Magazine* and the following associates: John MacKovace, B.A., Lester P. Aurbach, B.A., Helen A. Buchman, M.A., and Jerome R. Peskin, M.A. 8°, cloth, 699 pp., with 327 illustrations. Cleveland: Occupational Hazards, Incorporated, 1943. \$10.00.

This volume constitutes in a way an encyclopedia of industrial medicine. The text is divided into twelve divisions falling into two major classifications — industrial diseases and hazards, and safety provisions against accidents. Special reading bibliographies are appended to each subject. A valuable appendix on the classification of potential hazards by chief industries concludes the text. A large comprehensive index makes available all material contained in the volume. The work should prove of value as a ready reference source to all those interested in public health and industrial medicine.

The Principles and Practice of Tropical Medicine. By L. Everard Napier, F.R.C.P. (London), consultant to the Secretary of War, visiting lecturer on tropical medicine, Army Medical School, and visiting lecturer on tropical medicine, Harvard Medical School. 8°, cloth, 917 pp., with 195 illustrations and 32 tables. New York: The Macmillan Company, 1946. \$11.00.

This new textbook on tropical medicine is directed wholly for clinical and preventive application. The author has attempted to give an accurate and concise account of the more important tropical diseases from the viewpoint of epidemiology, etiology, pathology, symptomatology, diagnosis, prevention, treatment and prognosis, and discusses in a general way such relevant subjects as methods of mitigating the effects of a tropical climate, nutrition and anemia in the tropics and snakes and snake bites. The material is well organized, and many of the subjects are preceded by a short, historical paragraph. Selective lists of references are appended to each subject. Good indexes of subjects and authors are appended to the text. This new textbook by an outstanding authority should be in all medical libraries and the libraries of physicians interested in tropical medicine.

Public Baths and Health in England, 16th-18th Century. By Charles F. Mullett. Supplement No. 5 to the *Bulletin of the History of Medicine*. 4°, paper, 85 pp. Baltimore: Johns Hopkins Press, 1946. \$1.50.

This historical monograph is well documented, with references to the popular literature of the period. Appended to the text is a bibliography of books and pamphlets on the subject that should be of value to all interested persons. This monograph should prove valuable as a reference source on the subject.

An Introduction to Essential Hypertension. By Richard F. Herndon, M.D. 8°, cloth, 88 pp. Springfield, Illinois: Charles C. Thomas, 1946. \$2.50.

In this small book the author has presented a concise statement of what seems to be the present concept of hypertension in such a way that the ordinary practitioner of medicine can use it as a text for first reference. Following a definition of hypertension, the various aspects of the condition are considered in the following order: etiology and mechanism, physiology, pathology, clinical aspects, prognosis, diagnosis and treatment. For those who wish to pursue the subject further, the author has given as footnotes one hundred and thirty-nine pertinent references. This small volume should prove useful to the practicing physician.

Skin Diseases in Children By George M. MacKee, M.D., and Anthony C. Cipollaro, M.D. 8°, cloth, 448 pp., with 225 illustrations. New York: Paul B. Hoeber, Incorporated, 1946. \$7.50.

Skin diseases in children are extremely interesting and often present entirely different pictures from those caused by the same cutaneous disturbances in adults. The need of such a book as this is evidenced by the popularity of the first edition. The book is well written, and the print is excellent; the illustrations are numerous, depicting quite well the entities represented. There are several noteworthy chapters, especially those on allergic dermatoses, contagious diseases and syphilis. Certain other chapters, such as the one dealing with vesicular and bullous diseases, are lacking in the completeness expected in a book of this type, since the diseases discussed are fairly frequent in infants and children. It is a valuable reference book for the student, general practitioner and pediatrician.

The Diagnosis of Nervous Diseases By Sir James Purves-Stewart, K.C.M.G., C.B., Knight of St. John of Jerusalem, M.D. (Edin.), F.R.C.P. Ninth edition. 8°, cloth, 880 pp., with 358 illustrations. Baltimore: The Williams and Wilkins Company, 1945. \$11.00.

The ninth edition of this widely read book contains a considerable number of changes, but not so many as the author originally planned. He came to this country to evaluate American neurology during the war, and much of the text was revised with the aid of friends during his visit. New illustrations were furnished to replace some of the old, and the book was completely re-edited. Unfortunately, all this labor ended in disaster, for the new illustrations and fresh references, along with some of the text, were sunk in the mid-Atlantic by enemy action. The author was on another ship and therefore escaped. In spite of this setback, which might well have overwhelmed a less formidable person, the author made a further revision after returning to England, which resulted in the present text. There are enough changes to justify a new edition, and this volume will be widely welcomed by neurologists and medical students. It can be strongly recommended as in the past and is a welcome addition to the neurologic literature of the present day.

Gastro-Enterology Volume III *The liver, biliary tract and pancreas, and secondary gastro-intestinal disorders* By Henry L. Bockus, M.D., and colleagues. 8°, cloth, 1091 pp., with 427 illustrations. Philadelphia and London: W. B. Saunders Company, 1946. \$11.00.

This is a valuable book, half of which was written by Dr. Bockus and half by his colleagues in the faculty of the University of Pennsylvania Graduate School of Medicine, as in the two previous volumes. The style is pleasant, the book is well printed and bound, is accurate and complete and is beautifully and copiously illustrated. At the beginning of each chapter there is an index of contents, and a well chosen list of references is supplied at the end. About seven hundred pages are given to diseases of the liver and gall bladder, one hundred and twenty-five to diseases of the pancreas, sixty to gastro-intestinal parasites and one hundred to secondary affections of the gastrointestinal tract. This volume is especially welcome because of the recent increase in the frequency of diseases of the liver and of recent improvements in methods of diagnosis and treatment.

The material is so varied and extensive that it is difficult to single out special chapters for review. Many controversial subjects are treated with skill and good judgment, such as medical duodenal drainage, the medical treatment of gall-bladder disease, the question of early or late operation in the acute gall bladder, dyskinesia of the gall bladder, the surgery of so-called "silent gallstones," visceroptosis and the diagnosis and treatment of food allergy.

The complex physiology of the liver is described in clear and simple terms. Twenty-five liver-function tests are described, some of which are expensive and technically difficult, whereas only five or six of the simple tests are in routine daily use in most clinics. Possibly, the inclusion of so many tests that are only occasionally used may be confusing to the practitioner. Aspiration biopsy of the liver is described in half a page, this might be enlarged and a simple technique given, owing to its recent increasing use.

A large number of data on infective hepatitis and its epidemiology, transmission, pathology, early detection, diagnosis and prognosis are now becoming available from intensive study of the vast epidemics of World War II and will supplement and change the present chapters on acute hepatitis. Acute infectious hepatitis and acute yellow atrophy of the liver are described in separate chapters as different diseases, as in previous textbooks, but there is much recent evidence that they are simply different degrees of severity of the same disease.

The technical details of the treatment of patients with serious liver disease by carbohydrates, proteins and amino acids could be much improved both in acute hepatitis and in cirrhosis. Plasma transfusion, with its 5 or 6 per cent of protein, with a few grams of methionine a day, does not go far in restoring body protein reserves.

Lyons's biliary drainage is fully described, and a conservative estimate given of its value in diagnosis. Its use in treatment is not advised except in chronic infective cholangitis.

Biliary dyskinesia has been much discussed of late, and it is refreshing to find the statement, "As a working clinical diagnosis it should have a most insignificant place. We have been unable in a single instance to agree upon the diagnosis of biliary dyskinesia [in patients who have not been operated upon]."

In diseases of the pancreas the value of laboratory tests in the diagnosis of acute cases and the difficulties in chronic cases are pointed out.

There is an excellent short chapter on splenomegaly and its relation to diseases of the liver, heart and portal vein infections, hemolytic and other anemias, Hodgkin's disease, leukemia and so forth.

The chapter on functional diseases of the gastrointestinal tract is written by a neuropsychologist, and is much better than the usual chapter on these subjects. The value of psychologic and hygienic treatment is stressed in preference to drugs and placebos.

The book closes with a discussion of food poisoning of various kinds.

The work as a whole is excellent, and is highly recommended both to the specialist and as a reference book for the general practitioner.

Asclepius. A collection and interpretation of the testimonies By Emma J. Edelstein and Ludwig Edelstein. Volume I. 4°, cloth, 470 pp. Volume II. 4°, cloth, 277 pp. Baltimore: Johns Hopkins Press, 1945. \$7.50 (two volumes).

Asclepius in antiquity was the main representative of divine healing, — an important form of ancient medical treatment never opposed by ancient physicians, — and his worship played such a part in the final stage of paganism that he was judged the foremost antagonist of Christ above all other genuinely Greek gods. This work is devoted to a discussion of both aspects of the subject: Asclepius as the god of medicine and the Savior.

The first volume contains a collection of the ancient references to the life and deeds of Asclepius, his cult, images and temples; the second comprises an analysis of the material assembled in volume one. The material is restricted to written evidence and does not consider the cultural evidence portrayed in sculpture and painting and on coins. Although the work aims at an insight into the essence of Asclepius and of the cult attached to him, it also intends to provide a commentary on the whole ancient testimony on Asclepius preserved in books and on stone. The text is well written and printed on good paper, with a good type. This scholarly treatise should be in all medical-history collections, both public and private.

Surgical Treatment of the Motor-Skeletal System Part One *Deformities, paralytic disorders, muscles, tendons, bursae, new growths, bones, joints, amputations*. 4°, cloth, 641 pp., with 520 illustrations and a color plate. Part Two *Fractures, dislocations, sprains, muscle and tendon injuries, birth injuries, military surgery*. 4°, cloth, 639 pp., with 543 illustrations. Supervising editor, Frederic W. Bancroft, M.D. Associate editor, Clay R. Murray, M.D. Philadelphia: J. B. Lippincott Company, 1945. \$20.00.

This, as its name implies, is a two-volume treatise on the surgical treatment of orthopedic disabilities. It has been edited most ably by Drs. Bancroft and Murray, of Columbia University College of Physicians and Surgeons. The con-

The New England Journal of Medicine

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Volume 236

MARCH 6, 1947

Number 10

MILITARY SURGERY IN WORLD WAR II*

A Backward Glance and a Forward Look

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NEW ORLEANS, LOUISIANA

A DISTINGUISHED alumnus of Harvard University, Walter Lippmann, recently quoted what he identified only as the remark of a discouraged man: the lesson of history is that the lesson of history is never learned. Certainly, that statement holds for almost every phase of military surgery. We did not profit by the experience of World War I, much less that of previous wars, and in many respects it took us a discouragingly long time to comprehend the lessons that took form during World War II.

Perhaps the chief reason for our early difficulties in World War II is that we had not read the official British and American histories of World War I. Major General Philip Mitchiner, in 1944, confessed that sin of omission for the Royal Army Medical Corps, and it is open to question whether some American medical officers even now know that the histories exist. A partial explanation may be that the American history was published too long after the war had ended. By the time the first volume appeared, American physicians had dismissed from their minds most of the recollections of World War I, and in 1929, when the last volume appeared, a second world war still seemed inconceivable.

Trench foot, which is a responsibility of Command quite as much as of the Medical Corps, is an excellent illustration of a lesson that we should have learned and did not. In the spring of 1943 the campaign in the Aleutians produced several hundred cases of what was termed "immersion foot." In the following winter there were several thousand cases of what was unmistakably trench foot among the Fifth Army components fighting on the Italian Front. In the winter of 1944-1945 there were some 50,000 cases among the American forces fighting on the Western Front, the first concentrations of cases occurring during the critical days of the Battle of the Ardennes Bulge. The great majority of those cases, it is fair to say, should never have

occurred. Larrey, Napoleon's surgeon, had written a classic description of the condition, which contained many a useful warning, well over a century before. Trench foot, under other names, was reported in the Crimean, the Russo-Japanese and the Balkan wars. The British armies in Flanders and on the Somme had learned about it the hard way in World War I and had remembered the lesson through the years; trench foot was no problem among the British troops in World War II. We ourselves had had the experience in the Aleutians to prepare us for Italy, and that in Italy to prepare us for the Western Front. In fact, in the summer of 1944 the débacle of the coming winter on that front was clearly prophesied by the Surgeon General's Office. It is small consolation to reflect that had the Pacific War required the invasion of Japan and Manchuria, where the conditions of winter fighting in Europe would have been duplicated, the incidence of trench foot would probably have been minimal for prophylaxis had been most carefully planned on both Command and Medical Corps levels.

Other illustrations can be mentioned only briefly. If, for instance, we had read of or had remembered the many and futile attempts in World War I to sterilize wounds by means of antiseptics, we should have known better than to put our faith in any extraneous substances, including the sulfonamides on which we leaned so heavily in the early days of World War II. If we had read nothing more than the report of the Inter-Allied Surgical Conference in Paris in 1917, we should have known and could have put into immediate practice all the essential principles in the management of war wounds that were finally learned after many months of costly experience in World War II.

Medicomilitary lessons, like strictly professional lessons, were also learned the hard way. The possibilities of body armor, for example, were discussed in considerable detail in the history of the American Medical Department in World War I. Protective devices were adopted in World War II by the Air Force, with considerable savings in deaths and

*Presented at the Ether Centenary, Massachusetts General Hospital, Boston, October 14, 1946.

†Associate professor of surgery, Tulane University of Louisiana School of Medicine.

Skin Diseases, Nutrition and Metabolism By Erich Urbach, M.D., associate in dermatology, University of Pennsylvania School of Medicine, and chief of Department of Allergy, Jewish Hospital, Philadelphia. With the collaboration of Edward B. LeWin, M.D., associate in medicine, Jewish Hospital, Philadelphia. 8°, cloth, 634 pp., with 266 illustrations and 112 tables. New York: Grune and Stratton, 1946. \$10.00.

In this new book Dr Urbach stresses the use of dietary measures in the treatment of dermatoses. The text is divided into five parts: the influence of nutrition on the physiology of the skin, nutritional causes of dermatoses, including food allergy, the influence of diseases of the gastrointestinal tract, liver and pancreas on the skin, and nutritional therapy of skin diseases followed by a series of nutritional tables. A bibliography of one thousand three hundred and seven references is carried throughout the text as footnotes to the various chapters. Indexes of authors and subjects conclude the volume. This book should be in the reference collections of all medical libraries and should prove of value to allergists and dermatologists.

Alcohol Reaction at Yale By Ernest Gordon. 8°, paper, 87 pp. Francetown, New Hampshire: The Alcohol Information Press, 1946. Single copy, \$1.00, ten copies, \$6.00, postpaid.

This pamphlet constitutes an argument for prohibition.

NOTICES

ANNOUNCEMENT

Dr Raymond Gelfman announces the opening of his office for the practice of internal medicine at 10 Chestnut Street, Springfield.

FOOD AND HEALTH CONFERENCE

On March 20 the North Metropolitan District of the Massachusetts Department of Public Health will present a Food and Health Conference in the auditorium of the Public Works Building, 100 Nashua Street, Boston. The morning session will be held from 10:00 to 12:00, and the afternoon session from 2:00 to 4:00.

This meeting has been planned for health workers in the district. Discussions on the psychiatric problems in dietetics, recent developments in nutrition research, techniques for teaching nutrition, sanitation and visual aids have been planned, and there will be four exhibits. All are urged to attend this meeting and learn latest information regarding nutrition and new techniques for teaching.

MASSACHUSETTS PHYSICIANS' ART ASSOCIATION

The Massachusetts Physicians' Art Association has been established to encourage and stimulate the interest of physicians in drawing, painting, sculpture and photography. Any member of the Massachusetts Medical Society is eligible to join the association and may do so by sending in the annual dues (\$2.00) to the treasurer, Dr Robert W. Buck, 5 Bay State Road, Boston. This sum is to cover the cost of notices of meetings and the expenses of the yearly exhibition, which will be held this year at the Hotel Statler in conjunction with the annual meeting of the Massachusetts Medical Society, May 20 to 22. It is planned to hold meetings in Boston each month in the winter, with informal talks or classes for those who wish to draw or paint. Notice of the meeting in March will be sent on receipt of the dues. Additional information, if desired, may be obtained from the secretary, Dr Somers H. Sturges, Massachusetts General Hospital, Boston 14.

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Tuesday, March 4, at 8:15 p.m. Dr Murray J. Shear, chairman of the Chemotherapy Section, National Cancer Institute, will speak on the subject "The Chemotherapy of Cancer." Drs. William Dameshek, Saul Hertz, Ira Nathanson and Arnold Seligman will participate in the discussion.

WINTHROP COMMUNITY HOSPITAL

The regular monthly meeting of the staff of the Winthrop Community Hospital will be held on Thursday, March 27, at 9 p.m. at the hospital. Dr Howard A. Hoffman will speak on the subject "Urologic Problems in General Practice."

NEW ENGLAND HEALTH INSTITUTE

The New England Health Institute will be held at the University of New Hampshire, Durham, New Hampshire, on June 16, 17 and 18. This will be the first meeting since the war. A comprehensive program is being arranged, and the speakers will include many of the outstanding health and education authorities in the country. Special attention is being given to the timing of the different sections so that similar subjects will not overlap.

The facilities of the University will be at the disposal of those attending. Rooms will cost from \$1.00 to \$1.50 per day, special provisions being made for married couples. The school dormitories will be conducted on a hotel basis. Meals will be served in the dining halls at an approximate cost of \$1.50 to \$1.75 per day. There will be a banquet on Tuesday evening.

Since a large attendance is expected, all who plan to participate should register early. More detailed information will appear in a later issue of the *Journal*.

THIRD AMERICAN CONGRESS ON OBSTETRICS AND GYNECOLOGY

The Third American Congress on Obstetrics and Gynecology will be held September 8 to 12, 1947, in St. Louis. The program will feature general sessions for all groups making up the Congress, as well as small individual group meetings and round-table discussions. The morning sessions will be panel-type presentations of the following subjects: anesthesia and analgesia, cancer, and cesarean section. The afternoon meetings of the medical section of the Congress will consider psychosomatic aspects of pregnancy, pregnancy complicating cardiac disease, diabetes and tuberculosis, recent advances in endocrinology. Round-table discussions from four to five o'clock daily will consider such topics as etiology of abortion, asphyxia, fibroids, prolonged labor, infertility, early ambulation, adolescence, treatment of abortion, genital relaxation, ovulation, the menopause, the cystic ovary, uterine bleeding, nutrition in pregnancy, gynecologic pathology, endometriosis and erythroblastosis.

INTERNATIONAL CANCER RESEARCH CONGRESS

The Fourth International Cancer Research Congress will be held in St. Louis on September 2 to 7. The Union Internationale contre le Cancer having accepted the invitation of the American Association for Cancer Research, the congress will be held under the joint auspices of these two organizations, with Dr E. V. Cowdry, professor of anatomy, Washington University School of Medicine, and director of research at the Barnard Free Skin and Cancer Hospital, serving as president. The State Department in Washington has approved of the congress, and official invitations will soon be sent to all foreign governments that are to be asked to send delegates.

Initial steps in the organization of the congress have already been completed. In addition to Dr Cowdry, Dr J. Godard, president of the Union Internationale contre le Cancer, and Dr W. U. Gardner, president of the American Association of Cancer Research, will serve as *ex-officio* members of the Executive Committee. The following personnel have accepted committee chairmanships: A. N. Arneson, St. Louis—Local Arrangements; S. Bayne-Jones, New Haven—Finance; C. W. Larimore, New York City—Exhibits; L. A. Scheele, Bethesda, Maryland—Governmental Liaison; M. G. Seelig, St. Louis—Publicity, and Shields Warren, Boston—Program.

Headquarters will be at the Hotel Jefferson, St. Louis, where some 300 rooms will be available for guests. In addition, other nearby St. Louis hotels have signified a willingness to make reservations on advance notification by those contemplating attendance at the congress.

(Notices continued on page xv)

figures are not available, I am convinced that the salvage in morbidity was even greater

THE BACKGROUND OF MILITARY SURGERY

Before discussion of how these improvements were brought about in World War II, it is well to consider the background against which military surgery must be done. The surgery of a modern war has been aptly defined as the surgery of trauma in epidemic proportions. The demand is so enormous that it can be met only by a closely co-ordinated, well integrated medical organization prepared to operate promptly, efficiently and simultaneously under widely varying conditions and in all parts of the world. The organization must be highly mobile, so that it can move with the battle, otherwise it will lose its usefulness. It must function without interfering with the battle, the first objective is to get on with the fighting, and to fail in it or to impede it would not be to the best interests of the wounded, either individually or en masse.

The medical organization must operate long lines of evacuation from the front, where injury occurs and first-aid measures are carried out, to the rear, where definitive treatment is given, and thence to the homeland, where final therapeutic measures are applied. At the same time it must be prepared to treat well toward the front lines both men who are so lightly wounded that they can be promptly returned to duty and those who are so seriously wounded that they cannot be moved farther without treatment, or who require without delay operations of such a character as to prohibit transport immediately afterward. The whole process of evacuation, in fact, must be conducted on the basis of the transportability of the patient, which is itself predicated on the character of the injury, the physiologic reaction of the patient and the therapeutic measures employed.

All the circumstances of war surgery thus do violence to civilian concepts of traumatic surgery. The equality of organizational and professional management is the first basic difference. The second is the time lag introduced by the military necessity of evacuation. The third is the necessity for constant movement of the wounded man, and the fourth — treatment by a number of different surgeons at different places instead of by a single surgeon in one place — is inherent in the third. These are all undesirable factors, and on the surface they seem to militate against good surgical care. Indeed, when the over-all circumstances of warfare are added to them, they appear to make ideal surgical treatment impossible. Yet this was not true in the war we have just finished fighting, nor need it ever be true. Short cuts and measures of expediency are frequently necessary in military surgery, but compromises with surgical adequacy are not.

A number of factors, some inherent in the military circumstances and others created by proper concepts

and derivative planning, overcame the obstacles to ideal surgery in World War II. The first of these was what might be termed the standardized pattern of trauma and of physiologic response to it. Most of the diagnostic confusions of civilian medicine do not exist in military surgery, although, naturally, I do not mean to imply that serious diagnostic problems are not involved. On the other hand, whether a wound is in the extremities or in the abdomen or chest, or is caused by a high explosive, a land mine or a jeep, the pattern assumes the same general characteristics, the physiologic response, whether actual or potential, can be assumed to be similar, and the therapy required, resuscitative as well as

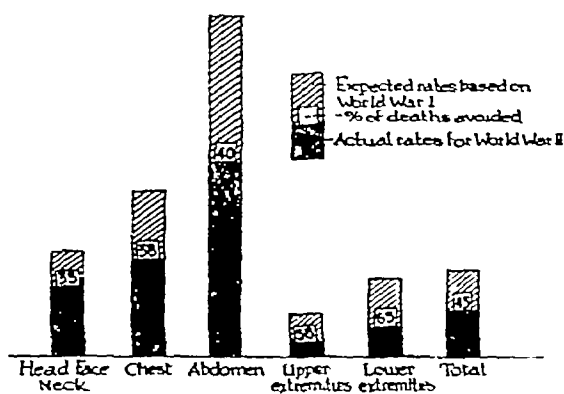


FIGURE 3 Percentage of Expected Deaths (Based on World War I Mortality Rates) Avoided in World War II

surgical, follows the same general lines. Furthermore, the United States Army consisted on the whole of a selected group of men, in the best years of their lives, in whom physical defects and chronic and degenerative diseases had been excluded by preliminary screening.

At least two planned factors also compensated for the unfavorable background of military surgery. The first was the principle of standardization or, as some might choose to term it, of regimentation. The framework into which the wounded man and the medical officer were alike required to fit was frankly rigid. But within the framework individual initiative was both permitted and encouraged, the ability and skill of the experienced surgeon were stimulated, and the less experienced surgeon was provided with training and guidance. As always, a general uniformity of technical procedure was regarded as essential, for reasons of safety, simplification and expedition, to make mass instruction of the medical personnel feasible and to permit standardization of basic equipment. I might interpolate that the directives and other means by which information and advice were disseminated were based on actual experience and represented the composite, carefully

wounds, by the end of 1943. On the basis of this experience, small though it was, and of several intensive studies on the lethality of weapons, it should have been apparent that great benefits might be derived from further developments in this field. Available statistics suggested that their adoption might reasonably be expected to reduce the number of men killed in action by 12 per cent and of those

obstacle to objectivity as prejudice or indifference. In the second place, a much longer time will be required to analyze all the medical data statistically and qualitatively. Representative samples, however, permit definitive conclusions and make clear the salvage that occurred in World War II, both absolutely and as compared with that in previous wars, in spite of our failure to learn the lessons of those wars.

From the Peninsular War, which began in 1808, through World War I, a period of more than a century, the proportion of men dying of battle wounds was almost halved (Fig 1). In World War II, which occurred only twenty-five years later, the proportion of men dying of battle wounds was again almost halved, although the number of wounded exceeded those in any previous war so recorded that estimates are possible. The absolute magnitude of these gains is not in any way invalidated by the unhappy realization that had we learned our lessons earlier, the salvage might have been still greater.

The case fatality rates of World War II, when examined from the standpoint of regional injuries, were from 25 to 50 per cent lower than those of World War I, which themselves showed a considerable reduction over comparable rates in the Civil War (Fig 2). For the sites that were potentially the most fatal — that is, the head, chest and

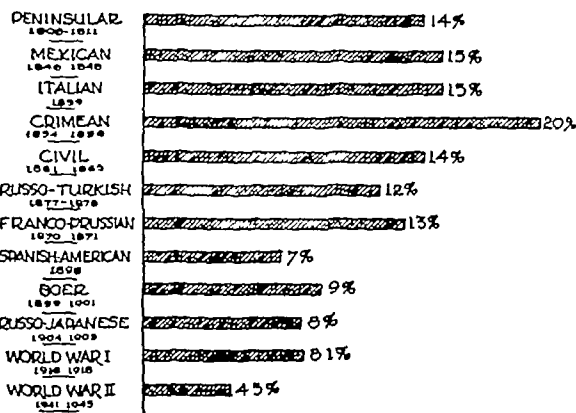


FIGURE 1 Mortality of Wounded in Various Wars

wounded in action by 8 per cent, but the Pacific War ended before body armor was in use on any front.

Convalescent camps, which were authorized for each hospital group in May, 1918, formed no part of the original planning for World War II and were provided, as in World War I, only after experience had shown that they were needed. Field hospitals for major surgical procedures were not planned in World War I for nontransportable patients who required prompt life-saving surgery, but were developed when the need became evident. It is ironic that in World War II the same evolution was necessary, although little reflection seems needed to make it plain that many of the injuries responsible for the greatest loss of life must be treated at this level if salvage is to be accomplished. At the end of the war, the field hospital still did not have tables of organization and equipment and, in the minds of administrative personnel, was still not fully accepted for the purposes it was serving, although it was the only available unit that could have been modified and made sufficiently flexible to meet them.

Whether a valid appraisal of the surgery in World War II is possible at this time is seriously doubtful. In the first place, we are still much too close to what has happened to permit comments that would be entirely objective, too many considerations, many of which have nothing to do with medicine, are likely to color our thinking, and under the circumstances overenthusiasm would be quite as much an

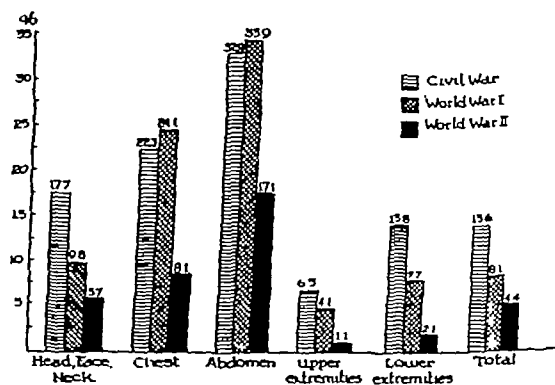


FIGURE 2 Mortality in Various Wars according to Location of Wound

abdomen — the rates in World War II were a half to two thirds below those in World War I.

Finally, to examine the gross statistics from still another standpoint, had the death rates after wounding that obtained in World War I been duplicated, almost 22,000 more deaths would probably have occurred in World War II (Fig 3). This is a total salvage of 45 per cent, and on a relative basis the calculated savings equal or exceed 35 per cent for every region of the body. Although comparable

to the realities. At the end of World War I specialized military practice ceased to exist with the rapid demobilization of the Medical Corps and, for all practical purposes, remained nonexistent during the interval between the wars.

Many of the difficulties that attended the effective utilization of specialists in World War I were avoided in World War II. Within three months of our entrance into the war there was established in the Office of the Surgeon General a Professional Consultants Division of full-time officers, with ranks eventually appropriate to their duties, although the administrative authority with which they were endowed was never fully adequate for their responsibilities. I need not repeat that the Surgical Consultants Division was headed by Brigadier General Fred W. Rankin, but I do want to pause to pay tribute to the native ability, the trained competence, the hard common sense and the uncompromising and unswerving honesty of purpose with which he carried out his duties, with the single-minded objective of providing for American soldiers the best surgical care any army has ever had.

As the war progressed, consultants in the major specialties, and usually in the subspecialties, were eventually appointed in every service command in the Zone of the Interior and in the Mediterranean and European theaters. The system, most regrettably, was never fully implemented in the Pacific, partly because of shortages of personnel and partly because of the deliberate postponement of the major effort in that area until the conclusion of the war in Europe. These consultants were selected with the utmost care, on the basis of training, ability, accomplishments and professional eminence, as a Boston audience need not be reminded, since the chief consultant for the Mediterranean Theater was Colonel Edward D. Churchill and the chief consultant for the European Theater was Brigadier General Elliott C. Cutler. From the medical standpoint, these were the important theaters, and Colonel Churchill and General Cutler exemplified to the highest degree the value of the consultant system and the possibilities of accomplishment within it.

The function of the surgical consultants was rather loosely defined as the promotion of the highest standards of medical practice within their areas of responsibility. They fulfilled it not primarily by the development of policies, but by the effective utilization and the continuing assessment and reassessment of specialized surgical personnel. When qualified personnel were properly assigned, policies developed of themselves. These surgeons were well trained men, many of them with long experience in civil life. Their concepts of surgery were correct. They were thoughtful as well as technically able. Their minds were open, and they realized the importance of changing their original convictions in the light of altering developments and cumulative experience.

They were widely distributed and traveled widely, so that their influence spread in ever-widening circles. It is no paradox to say that although most of them did no surgery and treated no patients in the course of the whole war, they were responsible for incalculable savings of life and limb.

SURGICAL ADVANCES IN WORLD WAR II

No major revolutionary changes in surgical practice were introduced during World War II. On the other hand, because of the enormous, concentrated surgical experience, principles were rapidly established — and are now being applied in civilian practice — that in the ordinary course of events would have taken years to establish. Furthermore, as the war progressed, there was an extraordinary appreciation, as well as a remarkably intelligent application, of fundamental principles so adapted as to meet the exigencies of military surgery. We were slow to learn some lessons and slow, perhaps, to utilize our experiences, but eventually certain concepts in the various fields of surgical endeavor became more clearly defined and their technical application became more general, with progressive improvement in mortality and morbidity rates.

The major advance, which underlay the progressive improvement in results accomplished as the war progressed, was the concept of phased wound management developed by Colonel Churchill in the early days of the Mediterranean fighting. This principle recognized the factors in the military environment that precluded ideal surgical practice and compensated for them by a rational timing of surgical measures to conform, in general, with the tactical necessities of the military situation. Its three phases were as follows: initial wound surgery, a function of advanced hospitals in the Army area, which was concerned with surgical procedures designed to save life and prevent or eradicate wound infection, reparative surgery, a responsibility of general hospitals in the Zone of Communications, which was concerned with procedures designed to shorten the period of wound healing, restore early function and minimize ultimate disability, and reconstructive surgery, a function of general hospitals in the Zone of the Interior, which was concerned with the correction of deformities and with rehabilitation in general.

The first and second phases of this plan took advantage of established principles of wound healing. From a military standpoint the entire concept was based on the fact that shortly after the first phase most patients, except those with penetrating wounds of the chest and abdomen, are safely transportable, whereas immediately after the second phase they become nontransportable for periods varying from a few weeks in cases of soft-part wound to several weeks in cases of fracture. By proper co-ordination of the three phases of this plan in time and space,

arrived at conclusions of many surgeons rather than the whims and practices of a single surgeon or one group of surgeons

A second compensatory factor was the precise definition of the function of each echelon in the chain of evacuation, from the first aid given on the battlefield by medical corpsmen to the reparative surgery performed in the general hospital at the base. Each procedure was timed and graded in relation to the whole picture, including the tactical situation, the particular point in the chain of evacuation and the wounded man's own status. Hospitals were designed and equipped for surgery of varying degrees of urgency and magnitude, with due consideration of the necessary duration and other requirements of postoperative care, and were strategically placed with reference to those considerations. Professional personnel were distributed in accordance with the function of the installation and the type of surgery to be performed. It is to the credit of a profession of individualists that almost every man submitted to these medicomilitary disciplines, recognized their necessity and justice, and confined himself to the job he was assigned to do where, when and as he was directed to do it.

Regimentation was based on fundamentally sound principles. The directives provided, for instance, that except for maxillofacial and cranial injuries, all wounds must be left unsutured after débridement, that all amputation stumps must be left unsutured, that transportation casts must be split or bivalved as soon as the plaster was dry and that injuries of the large bowel must be treated by exteriorization. Undoubtedly the transgression of any of these directives would have been practical and safe in numerous selected cases, but not much reflection is needed to make clear the folly of permitting the privilege of selection under combat conditions to thousands of surgeons who had been trained under varying schools of surgical thought and who were of varying degrees of ability and experience.

It was also necessary to view certain elective procedures in the cold light of military realism. What is good practice in civilian surgery is not necessarily the best practice, or even good practice, in military surgery. It was estimated, for example, that over a two-year period, 425,000 hospital days (approximately 1192 man years) were saved, and a corresponding amount of manpower time was made available, by the limitation of the treatment of pilonidal cyst and sinus to simple incision and drainage, or by the withholding of surgery altogether. Likewise, large savings were made and a great many difficulties circumvented by the adoption of conservative policies in the management of hydrocele, internal derangements of the knee and herniated nucleus pulposus.

Perhaps the most striking illustration of the necessity of detailed planning and of the value of uniformity of organization is supplied by the processing

of injured men on their return to the Zone of the Interior. For a period of some six months casualties from overseas were received at the ports at the rate of about 1000 a day. For a few months they numbered almost 2000 a day, and a large ship, such as the *Queen Mary*, might transport as many as 3000 at a time. Yet day after day, within an average of seventy-two hours of their arrival, most of the injured men were on their way by train or plane to the general hospitals selected as appropriate for them after assessment of their specialized needs at receiving hospitals on the coasts, procurement of authorized bed space from Washington and as much consideration as possible of the proximity to their homes of the hospitals to which they were sent. A triage of such monumental proportions would have been a remarkable achievement no matter how it was accomplished. That it was carried out with minimal errors in assignment and with no accidents of any consequence is as much a tribute to the planning of this special operation as it is clear-cut proof of the necessity for standardization of procedure.

The competent performance of the surgical personnel who participated in World War II undoubtedly had more to do with the surgical results achieved than any other single factor. That performance was made possible, in turn, by the increased availability of such personnel, in comparison with World War I, and by proper assignment.

The principles of specialization, as the term is understood today, had scarcely developed when the United States entered World War I. The Surgeon General, however, showed his awareness of the trend and took official cognizance of it by the appointment of a civilian specialist to advise him concerning surgery and the surgical specialties. This officer, who entered the Army with the rank of major and who served only part time, was responsible for the later selection of an advisory board, quite loosely organized and appointed on a geographic as well as a professional basis. At the same time, consultants in major specialties and subspecialties were appointed to overseas hospitals and units.

Although these concepts represented a real advance in military surgery, the theory of specialization was never fully translated into practice during World War I. The original development was undirected and unwieldy, and for a time the basic specialties of medicine and surgery were almost submerged by the independent mushroom growth of the subspecialties. Furthermore, the criteria of classification of specialists were elementary — they could hardly have been otherwise, for the modern system of residencies was practically unknown and the first of the qualifying boards did not come into existence until 1916. As a result, the applicant for a commission was graded chiefly on the basis of his personal statement of his qualifications and training, which, as might have been anticipated, sometimes bore little resemblance

valuable work, to which I am glad to pay my own personal tribute, is undoubtedly familiar to all. Nonetheless, from the standpoint of military surgery, it never completely succeeded in accomplishing its objectives, because of the barrier between military surgeons and civilian investigators that was never completely crossed on either side. Liaison existed between the Army and the various subcommittees of the National Research Council, it is true. Data from the field were supplied to the civilian investigators within the limits permitted by security regulations. Security regulations, unfortunately, were too often interpreted and applied with extreme severity, and medical documents that would have been of the greatest usefulness to research workers were classified far beyond the limits required by military security. Reports were made to appropriate subcommittees by occasional surgeons returned from overseas, and an occasional observer from the Council made surveys in the field. But complete integration of ideas and purposes was almost never achieved — not through any fault of personnel or through any lack of desire, but because of the initial setup. The failure was fundamentally due to the artificial and fallacious concept that a military problem could be detached from its military background, solved as an abstract problem in a civilian laboratory by civilian investigators who had no contact with it at its point of origin, and handed back to the military surgeons, completely solved and accompanied by appropriate therapeutic recommendations. Working in their own airtight compartments, civilian investigators naturally could not develop a true concept of the background of military surgery, which differs in many respects, as emphasized above, from civilian surgery. Nor could they ever fully understand the special necessities of military surgery or its special urgencies. It is extremely significant, and indicative of their medical competence, that the civilian investigators themselves realized these handicaps. In its final report in September, 1944, the Subcommittee on Surgical Infections and Burns recommended that thereafter such projects be carried out by qualified groups in the Services and that future civilian projects be limited to laboratory and other studies that could not be conveniently carried out in military hospitals.

The slow development of an optimum method for the treatment of burns is an illustration of the lack of integration of research studies and military surgery. Authoritative pronouncements were badly needed. In 1939, at the beginning of the war, tannic acid was the most widely used of all local agents. It was not satisfactory, but no other of the multiple methods then in use was considered any better. In October, 1942 the Subcommittee on Burns of the Division of Medical Sciences of the National Research Council, in response to a communication from the Surgeon General, recommended that the Army postpone further purchases of tannic acid

until additional information could be obtained. During the following month, in spite of a statement by the chairman early in the discussion that tannic acid jelly should not be used for either first-aid or definitive therapy, the tanning (eschar) treatment was recommended by the subcommittee for certain rather large categories of burns, and it was not until July, 1943, that the discontinuance of all escharotics was recommended and the substitute recommendation was made that first-aid measures consist only of the application of an oily, nonadherent agent, such as petrolatum.

By the time this conclusion was reached, the Surgical Consultants Division, on the basis of clinical experience in the North African Theater of Operations, which had clearly proved the ineffectiveness and actual danger of the eschar treatment, already had in preparation and on its slow way through channels a circular letter forbidding the use of any tanning agents and recommending simple pressure dressings, whose effectiveness had first been mass tested in the Coconut Grove fire in November 1942.

The evolution of recommendations concerning the use of chemotherapeutic agents was similarly slow. In July, 1940, the Subcommittee on Surgical Infections, in collaboration with the Committee on Therapeutics and Other Agents, had recommended the oral prophylactic administration of some sulfonamide drug as soon as possible after injury, as a means of preventing infection. It was reluctant to advise the local use of these drugs because, in spite of lay and professional enthusiasm for the practice, no adequate data were available to justify such treatment. Eventually, however, in response to an urgent request from the Surgeons General of the Army and Navy for a ruling, local chemotherapy was recommended. As a result of these recommendations, the individual first-aid kit was provided with sulfonamide tablets for oral use and with dusting powder for use in wounds.

When funds became available to the National Research Council, controlled studies were instigated under its auspices and were carried out by competent investigators in civilian hospitals in more than 2000 cases of traumatic wounds. The conclusion was reached, after the first 1000 cases had been analyzed, that when predisposing factors exist for the development of infection in accidental wounds, the use of chemotherapeutic agents in any combination and by any route does not prevent its development, although systemic therapy is probably of value in preventing invasive sepsis. In its final report, in September, 1944, this conclusion was retained, but the subcommittee declined, because of the differing conditions in civilian casualties and battle casualties, to institute comparisons, nor would it make any recommendations for the use or the omission of bacteriostatic drugs as prophylactic agents in the prevention of local infection in war wounds.

a close approach — perhaps the closest approach possible — to ideal methods of wound management was achieved within the limits of a military setting.

It proved possible to apply this principle of phased surgery to virtually every type of wound. Colonel Churchill himself admirably explained its application to thoracic surgery in World War II, in which, as he noted, the lung rather than the pleural space had become the focus of medical attention. In this type of surgery, he continued, two phases had to be recognized: physiologic disturbances and infection. The former required immediate correction in the most forward installation possible, sometimes by surgical measures; infection could occasionally be eliminated at the same time, but only incidentally. In general, the proper time to manage infection was within three days to six weeks after injury, and the place to correct it was an installation to the rear.

The phased management of abdominal injuries involving the large bowel required, in oversimplified terms, exteriorization of the injured segment in a forward installation, with subsequent closure of the colostomy in an installation in the rear. The phased management of fractures implied débridement of the wound and immobilization for transportation purposes in a forward installation, with later precise reduction and wound closure in a rear installation. Peripheral-nerve injuries, according to this principle, were débrided at initial surgery and sutured within an optimum period after delayed wound closure either overseas or in the Zone of the Interior, usually depending on the availability of transportation. Head and spinal-cord injuries and all other types were managed by similar temporal and spatial concepts.

Even the concept of resuscitation — ably developed in the Mediterranean Theater by Colonel Henry K. Beecher and based on a newer knowledge, largely provided by him and his associates — was phased, its objective being to present to the surgeon a patient who would be as favorable an operative risk as possible. Time does not permit a discussion of the important role played by this group of physicians in the delineation of the respective places of plasma and whole blood in resuscitation, in their bringing us back to sanity in the use of morphine (for which, they showed, a cigarette is sometimes an excellent substitute) and in anesthetic methods in wartime, a consideration of which would be peculiarly appropriate at this time and place.

A matter that statistics do not show and that deserves far more than the passing comment possible is the new approach to rehabilitation and reconstruction characteristic of surgery in World War II. Maxillofacial surgery achieved apparently impossible results, as did surgery of the hand. Programs of rehabilitation were designed for deaf and blind patients and for those who had lost limbs. The paraplegic program was not only a medical triumph and a shining illustration of the humanity with

which the science of surgery can be practiced but also a brilliant example of how co-operative medicine should be practiced.

RESEARCH ACTIVITIES IN WORLD WAR II

The research activities of World War II, brilliant as many of them were, furnish another excellent example of the lessons that we failed to learn from World War I. Important advances were made in various fields, but they were made late, after many hesitations and false starts, and in retrospect, it is easy to see how many opportunities were lost.

Significant information was obtained in World War I by research studies in overseas theaters concerning shock and hemorrhage, and by similar studies in this country regarding empyema. The data thus obtained were of great value in furthering knowledge of these subjects. Yet in spite of that experience, the policy in the early days of American participation in World War II discouraged clinical investigations in Army hospitals, research problems being referred to the National Research Council for investigation by civilian workers. The barrier thus set up was never completely crossed and was the chief reason for the delays and other inadequacies that attended the research problem throughout most of the war.

As the war progressed, the original policy discouraging research in Army installations was necessarily modified, and studies on special problems by small groups of investigators in the field proved feasible and valuable. Some of the studies carried out by members of the staff of the Massachusetts General Hospital and of the faculty of Harvard University provided information of the greatest value concerning the physiologic responses to shock, the bacteriology of wounds, the indications for transfusion in war surgery and, as mentioned above, the respective areas of usefulness of plasma and whole blood.

Isolated studies by individuals also frequently proved valuable, but many of them were invalidated by the lack of scientifically planned controls, and most represented an unnecessary waste of time, effort and personnel. During the war the Army Epidemiological Board had repeatedly shown what could be achieved by an organization prepared to function as soon as and wherever the necessity arose, and that board — and this is significant — functioned directly under the Secretary of War, with all the prestige and advantages of his authorization. It was not until August, 1945, when the great need and the great opportunity alike ceased to exist, that the Army Medical Research Board, with proper clinical representation, was finally set up in the Surgeon General's Office.

So much for the Army side of research during the war. Parallel, but seldom co-ordinated or integrated with it, was the effort of the Division of Medical Sciences of the National Research Council. Its

someness, an army in the field cannot operate, the inevitable result was a wastage of trained personnel that became increasingly acute as the war went on and that, had it lasted longer, might have been reflected in the care of the wounded. The problem was solved to some degree by the assignment of appropriate specialists to the points at which they could be most useful and by the concentration of patients with special types of injuries in centers equipped and staffed for their care, shortages of critical personnel, however, were always troublesome, and some of them were artificially created.

Such a situation must be avoided in the future. The medical profession is fully committed to the principle of specialization. It was employed in World War II far more extensively than in World War I because of two tendencies that had taken form in the interim between the wars. One comprised the efforts by civilian medical schools and hospitals to improve and standardize medical specialization by the provision of residencies and other facilities for postgraduate medical education. The other was the certification of specialists by the various qualifying boards. Neither of these tendencies, as already pointed out, existed prior to World War I, and it was the reservoir of specialists created between the wars that made possible the specialized and highly competent medical care given the wounded in World War II.

The philosophy of specialization in medical practice was based on too firm a foundation to have been overturned by a temporary, albeit catastrophic, interruption. The framework of its implementation, as a matter of fact, was actually strengthened by the experiences of the war and the performance of the specialists themselves. Specialization has now received legal recognition. It has been written into the laws governing the Veterans Administration, which, as a result, is providing for its charges medical care of a quality that it has never before provided. Equally strong efforts are now being made to continue specialization as an Army policy. The responsibility of the certifying boards and of teaching hospitals and medical schools, therefore, seems to be heavier than ever before, and the leaders in graduate educational endeavors must take full cognizance of the fact.

On the other hand, the policy of specialization must be applied with discretion and, so far as the Army is concerned, with understanding of military conditions. During World War II, as in every previous war, medical officers of the Regular Army necessarily assumed administrative positions. Their training had presumably fitted them better for those posts than it had for specialized professional service, whereas the civilian components of the Medical Corps were in most instances untrained for administrative posts, in which their specialized training and experience would have been wasted. Generally speaking, this is a sound policy. On the

other hand, the experience of World War II amply demonstrated the fallacy of the assumptions that a medical officer trained in a peacetime army was a priori fitted to assume a key administrative position during war and that a civilian surgeon necessarily lacked the qualities of leadership, judgment and vision required for it.

The degree of specialization to be required in the future Regular Army is difficult to determine at present. The size of the future military establishment is still undetermined, and specialization to be practiced effectively, requires concentrations of clinical material. The wisest plan may be for the Medical Corps of the Regular Army to provide the administrative structure and the general care of the troops, as well as the medicomilitary planning and training operations, leaving specialized hospital care to be supplied by a system of civilian consultants or of integrated federal medical service. The important consideration at present is not how the specialized care is to be supplied but that its necessity be recognized and, at the same time, the pitfall of too narrow specialization be avoided. It must also be constantly borne in mind that specialized practice emphasizes remedial medicine and that the Medical Department is a great deal more than a salvage service. The practice of preventive medicine and the planning for future operations are even more vital functions in war than in peace. In both its most valuable function is its advice to command.

The problem is not quite so simple, however, as this statement of policy implies. Other considerations are linked with purely military matters. During the war obvious shortages of personnel developed and certain specialists were always in critical supply, but the opinion was that once the war had ended, these difficulties would resolve themselves. They have not resolved themselves, nor does any thinking physician believe that they are likely to, at least under the system by which federal services are now operated.

It would be difficult to imagine a more wasteful and extravagant plan, for example, than the one on which hospitalization in this country is currently conducted. We have a system of private hospitals, of widely varying size and excellence. We also have, exactly as we had at the beginning of World War II, a fourfold, parallel system of federal hospitalization, including separate establishments for the Army, the Navy, the Veterans Administration and the Public Health Service, with confusion worse confounded by the maintenance of separate installations, sometimes only a few hundred yards apart, for the Air Forces and the Ground Forces. What this means in terms of wastage of material and equipment and money is perfectly obvious, what it means in terms of wastage of professional personnel particularly of specialized personnel, may not at first glance be so clear.

The reports from Pearl Harbor seemed to indicate that both local and systemic chemotherapy was highly effective in battle wounds. Undoubtedly much of the early reliance on chemotherapy was due to that experience. In the enthusiasm over the results, however, many Army and Navy surgeons, as well as many civilian surgeons, lost sight of the emphasis that these reports also placed on adequate surgery. As early as 1943, numerous reports from the Mediterranean Theater, later supplemented by reports from the European Theater, substantiated the conclusions of the National Research Council workers regarding the ineffectiveness of local chemotherapy in wound infections. Soon afterward, a directive was issued forbidding the local use of the sulfonamides, and they were no longer placed in the first-aid kit in any form.

It is pleasant to be able to report that most of these errors and hesitations were avoided in the study of penicillin and streptomycin. The investigations were set up by civilian investigators working under the National Research Council, and the projects, when they were fully operative, were taken over and carried on with great success by members of the Army Medical Corps specially assigned to and specially qualified for the work. The result was that when these agents were made generally available, the principles of usage had been clearly established and their limitations and risks had been equally clearly defined. Both projects represent the type of integrated civilian-military research that, unfortunately, so many other projects do not, and point the way to future planning for research in a similar emergency.

THE IMPLICATIONS OF MILITARY SURGERY IN THE POSTWAR WORLD

I hope that nothing that has been said will be interpreted to mean that the Medical Department of the United States Army did not do a competent job in World War II. It functioned superbly. No soldiers in any war ever had such care as was given to the American soldiers in the last war. If, on the other hand, what has been said seems to indicate that the formulation of policy of military surgery in World War II was a matter of evolution, it must be admitted that the implication is correct. The Medical Corps, like most other branches of the Army, entered on the emergency of World War II quite as unprepared as it had been at the outbreak of World War I. In large measure this was not the fault of the Surgeon General. For one thing, the American public, as always during years of peace, had shown no enthusiasm, but rather apathy and sometimes actual hostility, for planning for another war. Congress, the source of funds, had followed the same line.

Furthermore, and even more important, successive surgeons general of the Army, whatever their convictions, had little or no authority to act on them. In the midst of World War I, over the protests of

the Surgeon General then in office, the Medical Corps of the Army, previously an entity in its own right, had been placed under the Service of Supply (later the Army Service Forces) and by this move, in spite of his sole responsibility for the health and medical care of the Army, the Surgeon General had been cut off from direct access to the Chief of Staff and the Secretary of War. Professional personnel, for all practical purposes, was reduced to the status of rations and ammunition. As the Chief Surgeon of the American Expeditionary Forces protested when the change was made: "The present organization places a line officer of the General Staff in position to pass upon or present for higher consideration all matters of fundamental policy affecting the Medical Department. He can nullify the most carefully worked out program having for its object Medical Department efficiency." The Surgeon General, in short, could continue to raise his voice on medical matters, but he no longer had any certainty that it would be heard. He continued in this unhappy position in the interim between the wars and through most of World War II. By April, 1945, however, the anomaly of his status had given rise to so much confusion that it became necessary to clarify his duties and responsibilities by a War Department Circular, concurred in by the Secretary of War, who at that time assumed direct responsibility for the sick and wounded of the Army.

The anomalous position of the Surgeon General was responsible for many of the medical troubles encountered in World War II. Prestige cannot be established by regulations, rather, it is the product of successful achievement. Nevertheless, the position in which the Medical Department was placed in the organizational structure of the Army cannot be regarded as conducive to the enhancement of its prestige. The Surgeon General's advice might not be asked, even on matters that directly concerned the health and well-being of the troops. If it were requested or offered, there was no assurance that it would be accepted, translated into proper action or translated into any action at all. The situation demands correction. The Surgeon General must, of course, be subject in tactical matters to purely military command, but he must also again become master in his own medical house. His position must be so clarified that he can carry out his responsibilities and functions under the direction of a medically enlightened command, which is fully aware of the part played by the Medical Department in the actual business of warfare and which realizes, as Sir Alexander Hood has well put it, that "the medical services are the authorities on man and all that concerns him."

An important by-product of the anomalous position of the Medical Department in World War II was its lack of direct control over its own personnel. When that handicap was added to the structural organization without which, in spite of its cumber-

PROTEIN NUTRITION*

The Therapeutic Use of a Digest of Liver Protein, Especially in Patients with Cirrhosis of the Liver

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With the Assistance of Margaret A. Adams, Jean V. Harrison, and Mary A. Maloney

BOSTON

IN THE treatment of many diseases it is often desirable to administer a part or, occasionally, all of the patient's food in a liquid form. Such a liquid formula should satisfy the nutritional needs of the patient in a concentrated, easily assimilable form. Particular interest has recently been evidenced in food supplements designed for patients needing additional protein. A high-protein intake has been shown to be especially desirable in certain conditions, such as cirrhosis of the liver,¹ nephrosis,² peptic ulcer,³ healing of surgical wounds⁴ and burns⁵ and states of malnutrition due to restricted intake.

The supplement¶ described in this paper is derived from liver protein by partial hydrolysis. Investigations on dogs with low plasma protein concentration due to depletion have shown that the protein of beef liver is active in building plasma albumin.⁶⁻⁸ This activity is not so effective as that of beef serum and egg white but about the same as that of beef muscle and casein. Thus, it was assumed before study that this protein would be adequate to maintain nitrogen equilibrium or a positive nitrogen balance in human beings, and the following investigation supports this assumption.

In addition to adequate protein, an ideal liquid supplement should contain sufficient energy value to prevent utilization of the protein for fuel. The liver protein hydrolysate contains only a small amount of carbohydrate and fat so that if the patient's diet does not furnish sufficient calories, sugar or starch or some other source of energy may be added to the liver protein digest. The liver protein digest contains ample amounts of most of the well known fractions of the vitamin B complex and is also a good source of the less familiar members of

this group but contains no appreciable amounts of the other vitamins.

A supplement should be as palatable as possible and free from disagreeable side effects. The liver

TABLE 1 The Composition of Granular Liver Protein Digest.*

SUBSTANCE	AMOUNT per 100 gm.	AMOUNT IN DAILY DOSE (180 gm.)
Calories	354	640
Protein	55 gm.	100 gm.
Carbohydrate	33 gm.	60 gm.
Fat	0.9 gm.	1.5 gm.
Vitamins		
Thiamine	3.5 mg.	6.0 mg.
Niacinamide	22.0 mg.	40.0 mg.
Biotin	0.16 mg.	0.3 mg.
Inositol	75.0 mg.	128.0 mg.
Riboflavin	6.6 mg.	10.0 mg.
Calcium pantothenate	7.6 mg.	13.0 mg.
Folic acid	0.28 mg.	0.5 mg.
Pyridoxine	0.8 mg.	1.4 mg.
Choline	350.0 mg.	680.0 mg.
Available amino acids		
Arginine	3.5 gm.	6.0 gm.
Cystine	2.7 gm.	4.6 gm.
Glutamic acid	7.4 gm.	12.4 gm.
Histidine	1.6 gm.	2.7 gm.
Isoleucine	2.3 gm.	3.8 gm.
Leucine	3.8 gm.	6.3 gm.
Lysine	5.7 gm.	9.5 gm.
Methionine	0.9 gm.	1.5 gm.
Phenylalanine	1.9 gm.	3.2 gm.
Threonine	2.5 gm.	4.2 gm.
Tryptophane	0.4 gm.	0.7 gm.
Tyrosine	1.4 gm.	2.3 gm.
Valine	3.0 gm.	5.0 gm.

*From data furnished by the manufacturer except the protein content, which was determined in this laboratory and is slightly higher than that given by the manufacturer.

protein digest, flavored with chocolate, is palatable enough to be taken by most patients and, except for a laxative action in some cases, is without disagreeable side effects.

MATERIAL AND METHODS

Preparation and Composition of Liver Protein Digest

Liver protein digest is a dry, slightly hygroscopic, granular powder prepared by vacuum drying of a partial enzymatic (papain) hydrolysate of the liver pulp — the portion of the beef liver remaining after hot aqueous extraction of the anti-pernicious-anemia factor. The final powdered digest contains by weight

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†This study was aided in part by a grant, "In recognition of Dr. Francis W. Peabody's services to the Foundation" from the Ella Sachs Plotz Foundation.

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¶"Ledinac" prepared and kindly provided by the Lederle Laboratories, Pearl River, New York.

It has been conservatively estimated that the various governmental agencies supplying medical care will soon need half a million hospital beds. That is a third of the present hospital-bed capacity of the whole country. As the need for bed space multiplies, so will the need for professional personnel, particularly for specialized personnel, who cannot be supplied by the present system. Sane thinking therefore indicates the merger of the present separately maintained federal establishments, at least on the hospital level in the Zone of the Interior, which would reduce the needed professional personnel by 50 to 75 per cent, greatly increase efficiency of operation and greatly reduce costs. The conservation of specialized personnel, along with their efficient use, is one of the lessons that should have been learned for all time from the surgical experiences in World War II.

At present, from the standpoint of medical practice as well as in a number of other respects, we are acting from day to day. We have no plans and, worse, we have no principles to guide our course of action. Such a situation must not be permitted to continue. The surgical problems of World War II far exceeded in magnitude those of World War I. The problems of a possible third world war, about which we shall be criminally negligent if we are not entirely realistic, are likely to exceed to a staggering degree those of World War II. The end of World War II may indeed have marked the end of an era in military surgery, which for centuries had followed a pattern that, although progressively more demanding, was still essentially similar. Much of the knowledge we now possess, however, may become irrelevant and useless in this new era. There will necessarily be a new concept of war wounds. Radiation, blast and burn injuries of atomic origin will pose problems of management different from those hitherto associated with surgical care, and there must be a new concept of traumatic surgery in terms of regional injury.

Furthermore, the introduction of atomic weapons is likely to wipe out the old concept of echelons of combat and areas of security, and to bring civilians and military forces together into a single zone of combat. Atomic warfare is likely to cause an instantaneous flood of casualties, such as no battle

in the history of the world ever before produced. It will require the full use of all hospital facilities, on an over-all basis, with no wastage of beds, as well as the strategic placement of all equipment for general use as needed. Above all, it will require the mobilization of the entire medical personnel of the Nation on a disaster basis. There can be no distinction between military and civilian medical responsibility, for there will be no distinction between military and civilian injuries. It will require a mobility and speed of assignment of medical and surgical personnel such as has never before been necessary. There can be no more wastage of physicians. The problem, indeed, may be to keep the medical personnel of the country protected and alive and sufficiently uninjured to carry out their functions.

I should not like to end on this note. I do not believe that so dark a future will come soon, or that it is inevitable. But we should be lacking in realism and deserving of our fate if we did not face the possibilities frankly and take steps to forestall, prevent and prepare for disaster. Changes will be necessary: changes in the concept of medical education, changes in the methods of graduate education, changes in the plan of medical practice and changes in the relation and attitude of the civilian medical profession toward the federal medical services, including the Army and the Navy. To bring them about will take authority on a high level, which is now lacking on any level and which, when it is set up, must be exercised with wisdom and judgment and great discretion. Without medical statesmanship of a high order, these objectives cannot be attained.

Obviously, the experiences of World War II cannot be transferred directly to a possible atomic war. They must not, however, be discarded lightly. For the present, at least, they are all we have to go on. They supply some solid point of departure, in spite of the changes that must be made. The future of atomic warfare is uncertain, but the lessons of the last war will help, and certainly if we learn them, we shall be in a position of vantage that we have never before occupied at the beginning of any previous war.

In the 3 other normal subjects, nitrogen-balance studies were carried out after an initial period during which the patient received the 25-gm protein basic diet. The intake was 1900, 2500 and 4000 calories a day, depending on individual needs, and additional protein in amounts of 26, 50 and 46 gm daily respectively was supplied isocalorically by the liver protein digest.

A positive nitrogen balance was achieved in each case, and the level of plasma proteins remained normal throughout.

Plasma Protein Regeneration

In the normal group studied, no significant changes were observed in the plasma proteins,

edema had disappeared there was a gradual gain in body weight from 98 to 105 pounds. During the study the food and supplement furnished from 2000 to 3000 calories a day. A markedly positive nitrogen balance of about 20 gm daily was maintained during the entire period.

Liver Disease

Portal cirrhosis Nineteen patients in whom the diagnosis of portal (Laennec) cirrhosis had been made were studied. The past history in all revealed an excessive alcoholic intake and a food intake relatively low in protein and foods containing the vitamin B complex. The disease in these patients was roughly classified as mild, moderate and severe, on the basis of the duration of disease, physical examination and derangement of liver-function tests.

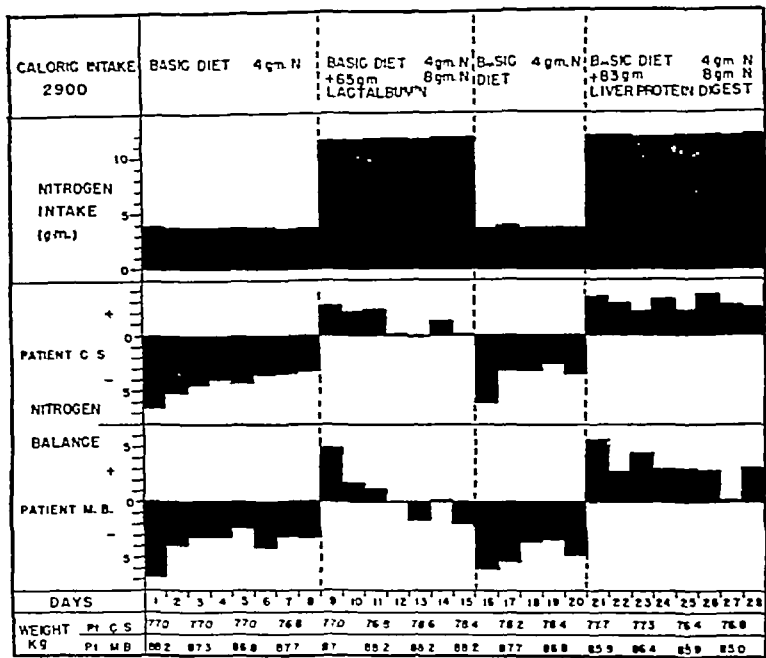


FIGURE 1 Nitrogen Balance Studies on Two Normal Subjects

which remained within the normal range throughout the study. This was also true of the patient with peptic ulcer and 3 patients with uncomplicated malnutrition. The results in liver disease are discussed below in connection with the other findings. The regeneration of plasma proteins was particularly striking in a patient with nephrosis, and this case is presented in detail.

L.P., a 38-year-old man with chronic glomerulonephritis and the nephrotic syndrome was given a diet containing 100 gm of protein and a supplement of liver protein digest containing an additional 100 gm of protein. On admission he had massive generalized edema, proteinuria and hypoalbuminemia. The proteinuria remained unchanged during the 50 days of study but, as shown in Figure 2, the edema disappeared, the body weight fell and the plasma albumin concentration rose from 1.5 to 3.5 gm per 100 cc. After the

(Table 2) In this connection the most valuable physical sign was the presence of ascites. Edema was present in only a few patients who did not have ascites. The liver size was not used as a criterion of the severity of the liver involvement in classification of the patients. Of the liver-function tests performed in this group, the cephalin-flocculation and thymol-turbidity tests had the greatest prognostic value. The bromsulfalein retention and the prothrombin time varied greatly and seemed to have little value in determining the severity of liver dysfunction or prognosis. The icteric index and serum bilirubin concentration were of importance only so far as they changed with the course of the disease and did not indicate the extent of permanent

54.5 per cent hydrolysate of the liver pulp, 37.8 per cent spray-dried malt and 7.5 per cent bitter chocolate

This preparation is naturally high in components of the vitamin B complex, with the exception of thiamine, which has been added. In Table 1, which shows the vitamin content as determined by the manufacturer, it can be seen that 100 gm of liver protein digest furnishes more than the National Research Council optimum allowances of thiamine, riboflavin and nicotinamide.⁹ Optimum values for the other components of the vitamin B complex have not been established, but moderate amounts of biotin, calcium pantothenate, folic acid and pyridoxine are present in this material. In addition, lipotropic factors, such as choline, inositol and methionine, are included.

Table 1 also shows the amino acid content of the liver protein digest. All the amino acids that have been shown to be essential in man¹⁰ are present.

The liver protein digest is easily suspended in hot water, although a precipitate settles on standing, this may be quickly resuspended by shaking. Usually, 180 gm of the digest dissolved in water to make 1 liter and containing approximately 100 gm of protein was given daily.

Nitrogen-Balance Studies in Normal Subjects

Food intake and nitrogen balance were studied in 5 normal persons in good nutritional status. Each received a basic diet containing 25 gm of protein and between 2000 and 4000 calories. Throughout the entire period of study the individual caloric intake was kept constant, and the protein studied was substituted isocalorically for carbohydrate. In 4 cases the activity of the liver protein digest was also compared with another protein of known biologic value. Daily determinations of the urine nitrogen were made by the micro-Kjeldahl method, and three-day or five-day determinations of the pooled stool by the macro-Kjeldahl method. Total plasma proteins and albumin globulin fractionations were determined by the Howe method.¹¹

Plasma Protein Regeneration

Plasma protein levels were followed in the 5 normal subjects, in 11 patients with portal cirrhosis of the liver, in 1 patient with nephrosis, in 1 patient with peptic ulcer and in 4 patients with uncomplicated malnutrition. The regeneration of the plasma proteins is discussed below.

Clinical Studies

Sixty-five patients received the liver protein digest daily over periods of one to seventy days. In 11 cases it was necessary to discontinue the study—in 3 because the disease had progressed to coma, in 3 because the patients refused to take the material, in 3 because of vomiting in 1 and severe diarrhea in 2 and in the other 2 because the patients were dis-

charged or transferred. Thus, 54 patients were studied, and the results of treatment are discussed below under the respective diseases.

Ten of the patients studied were placed on weighed diets and the caloric and protein intakes calculated. Most of the remaining patients received hospital diets, although a few were placed on special low-salt or Sippy regimes as required by the disease. Body weight was followed so far as possible in all patients. In patients with liver disease the serum bilirubin,¹² the cephalin-flocculation¹³ and thymol turbidity tests,¹⁴ the prothrombin time,¹⁵ the brom-sulfalein retention and the plasma protein concentration were followed.

RESULTS

Tolerance

Although the initial flavor of the liver protein digest is not distasteful, the preparation leaves a bitter liver taste in the mouth that to some is disagreeable. It was soon found that the psychologic introduction of this material as a medicine containing "liver and vitamins" obtained the co-operation and interest of the patients. A few patients, however, found the flavor so distasteful that the material could not be tolerated.

The laxative effect of the liver protein digest also limited its usefulness in some patients. This effect was particularly noticeable in patients who had gastrointestinal disorders associated with diarrhea, although even in some of these the diarrhea stopped after a few days of treatment with the liver protein digest. Most patients, however, noticed either no effect on their bowel habits or a slight increase in the number of bowel movements daily. This slight laxative effect could be ameliorated by urging frequent small feedings. Only one patient had diarrhea to such an extent that the digest had to be discontinued. The substance in the digest causing the laxative effect is not known but has been observed in the use of most oral liver preparations. It was certainly a major drawback to the usefulness of this protein digest in a few patients.

Nitrogen-Balance Studies in Normal Subjects

The results in 2 of the 5 normal subjects are demonstrated in Figure 1. These subjects were placed on a basic 25-gm protein diet, and after equilibrium or minimum negative nitrogen balance had been achieved, a lactalbumin preparation was given to raise the protein intake to 75 gm. After seven days these subjects were returned to the basic 25-gm protein diet for a short period, and a second trial period was then instituted by the addition of 50 gm of liver protein digest. The intake was maintained throughout at about 2900 calories. The amount of nitrogen retained during the administration of liver protein digest was even slightly greater than that during the administration of lactalbumin. Plasma protein concentrations remained at normal levels throughout.

revealed a long duration of the disease before the present admission to this hospital. Ascites improved in only 1 case, and in the other 4 repeated paracenteses were necessary. The plasma protein concentration was followed in 3 cases and showed little

by 5 patients with thermal burns. The data concerning these patients are presented in Table 7. All had severe burns. One patient (Case 36), with a third-degree burn of 46 per cent of the body surface, died on the thirteenth hospital day, nine days after the

TABLE 2 Classification of Cases of Cirrhosis

DEGREE OF CIRRHOSIS	CASE No	ASCITES	EDEMA	LIVER SIZE* cm	CEPHALIN FLOCCULATION	BROM-SULFALGIN RETENTION† %	THYMOL TURBIDITY‡	PROTHROMBIN CONCENTRATION %	ICTERIC INDEX
Mild	1	0	++	4	+	32	1.80	90	15
	2	0	0	6	0	32	1.32	45	35
	3	0	0	7	+	—	—	100	100
	4‡	++	++	5	0	20	1.10	—	40
	5	0	0	4	0	28	—	100	15
	6	0	0	3	++	—	1.77	—	25
	7	0	++	7	++	12	2.68	100	5
	8	0	+	7	++	12	2.68	—	35
	9	0	0	3	++	20	3.90	78	4
Moderate	10	++	++	1	++++	32	4.37	—	10
	11	+++	0	4	++++	44	2.09	89	100
	12	+++	+	4	++++	—	—	—	100
	13	++++	+	Not palpable	++++	28	3.40	100	6
	14	+++	++	10	++++	—	2.33	80	75
Severe	15	++++	++	Not palpable	++++	—	4.01	68	50
	16	++++	+	4	++	8	3.33	78	25
	17	++++	++	Not palpable	++	36	—	100	8
	18	++++	++	Not palpable	++++	—	4.06	—	17
	19	++++	+	Not palpable	++++	40	4.14	—	50

*Distance palpable below the costal margin.
†At forty five minutes after intravenous injection of 5 mg. per kilogram of body weight.
‡Normal range 0 to 1.68.
§This patient had a moderate degree of heart failure with chronic passive congestion.

change after treatment. The serum bilirubin concentration changed little during the period of treatment with liver protein digest.
Infectious hepatitis. Five patients with infectious hepatitis were given the liver protein digest in the same daily amounts as those given in cirrhosis of

initial administration of liver protein digest. In the others, who consumed variable amounts a day for periods ranging from thirty-two to seventy days, the nutritional status was either improved or maintained. In 2 patients (Cases 34 and 35) the liver protein digest was the chief source of protein during

TABLE 3 Calorie and Protein Values of Basic Diet and Liver Protein Digest Supplements *

CASE No	CALORIE INTAKE								PROTEIN INTAKE							
	5 DAYS	10 DAYS	15 DAYS	20 DAYS	25 DAYS	30 DAYS	35 DAYS	40 DAYS	5 DAYS	10 DAYS	15 DAYS	20 DAYS	25 DAYS	30 DAYS	35 DAYS	40 DAYS
16	1800	2500	2200	2500	2700	2700	2600	2200	130	160	140	150	210	200	200	200
17	2800	1800	2200	2300	1800				230	140	150	150	160			
11	1900	2500	2400	2700	2600				120	160	160	200	200			
3	2600	2700	2200						200	220	210					
8	2600	2600	2600	2700	2600				210	160	210	150	180			
5	2400	2300	2200						200	180	170					

*Daily averages in five-day periods

the liver. Rapid improvement after the initial phase of the disease was observed in all patients, but from this small series it is impossible to conclude that the liver protein digest influenced the course of the disease. It was well tolerated in all cases after the initial acute gastrointestinal symptoms associated with the disease had improved.
Burns.
The liver protein digest was taken as a food supplement in amounts from 95 to 540 gm. a day

the period of administration. In the others various supplements, both oral and intravenous, were used.
A patient (Case 35) in whom the liver protein digest was the chief source of protein for a month, improved more rapidly during this period than during that in which he had received other protein supplements in approximately equivalent amounts. One patient (Case 34) developed a rash that was at first papular, and then became pustular and disappeared soon after the liver protein digest had been discontinued. This was the only suspicious sign of

damage or the prognosis. The total protein and albumin-globulin fractionation were not determined in all cases but showed definite trends in each group. In the mild cases the plasma albumin concentration was above 3.35 gm, and the globulin fraction concentration was below 2.8 gm per 100 cc. In the moderate cases the albumin concentration was

below the costal margin in the midclavicular line in only 2 cases. It seems likely that in this group the enlarged livers were due to fatty infiltration and the disappearance of this fat accounted for the rapid decrease in size. The plasma protein concentration was followed in 4 patients. Two showed an increase of plasma albumin concentration of about 1 gm. per

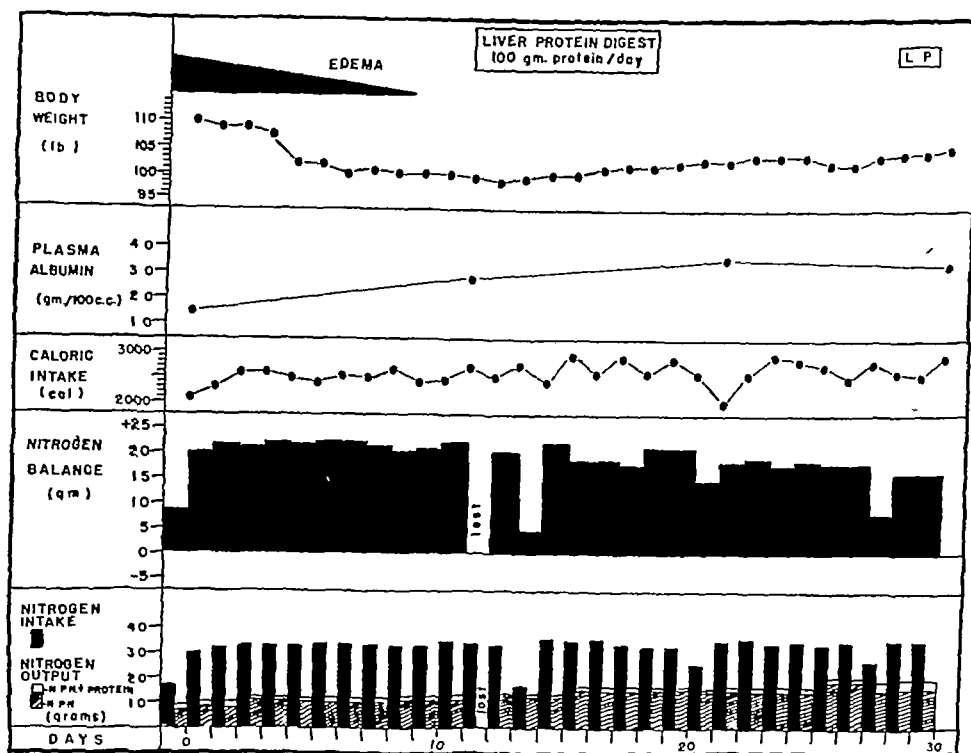


FIGURE 2 Essential Data in a Patient with Chronic Glomerulonephritis and the Nephrotic Syndrome

between 2.6 and 3.7 gm, and the globulin between 3.2 and 3.6 gm per 100 cc. In the cases classified as severe the plasma albumin was below 2.5 gm, and the globulin between 3.3 and 4.3 gm per 100 cc.

All patients received a daily supplement of liver protein digest containing 100 gm of protein in addition to a hospital diet supposedly high in protein and calories. No attempt was made to keep the fat low in these diets. In 6 cases the total caloric and protein intake was averaged for five-day periods from weighed diets (Table 3). The basic diet was planned to contain 300 gm of carbohydrate, 100 gm of protein and 50 gm of fat. The actual daily intake ranged from 1800 to 2800 calories and from 120 to 200 gm of protein.

Nine patients were classified as having mild cirrhosis. After receiving liver protein digest from twelve to thirty days, the improvement in this group was marked. Table 4 shows the most striking changes. The livers, which had been enlarged in all these patients before treatment, decreased in size after treatment and were palpable more than 1 cm

below the costal margin in the midclavicular line in only 2 cases. It seems likely that in this group the enlarged livers were due to fatty infiltration and the disappearance of this fat accounted for the rapid decrease in size. The plasma protein concentration was followed in 4 patients. Two showed an increase of plasma albumin concentration of about 1 gm. per

100 cc, whereas in the other 2 the albumin concentration remained constant or slightly decreased. In only 1 patient (Case 4) was there an increase in plasma globulin. The serum bilirubin concentration was elevated in 6 cases, in all of which the total bilirubin decreased to normal, although the direct reacting bilirubin remained elevated in 4.

In the 5 cases classified as moderate, 4 patients showed marked and 1 moderate improvement (Table 5). Ascites and edema decreased or vanished, and the liver size diminished. The plasma proteins were determined in 4 patients of this group, the plasma albumin concentration remained constant in 1 and was increased in 3. The globulin concentration increased slightly in 3 patients. The serum bilirubin determination was followed in only 2 cases, in which it decreased to normal total bilirubin concentration, although 1 patient continued to have an elevated prompt, direct bilirubin concentration.

In the group of 5 patients with severe cirrhosis, 3 died and the others showed only minimal improvement (Table 6). The past histories in these patients

and showed only slight improvement. The remaining 10 patients received the liver protein digest for nine to twenty-three days with moderate to marked improvement. Weight gains ranged from 1 to 10 pounds, averaging 6 pounds for a two-week period of treatment. The 3 postoperative patients showed rapid wound healing and weight gain. The patient with hemophilia had an ulcer on the left leg and was

in this group. In another patient, a seventy-five-year-old woman with a poor dietary history, the initial total protein concentration was 4.8 gm, with an albumin concentration of 1.71 gm per 100 cc. For fifteen days she received 100 gm of protein from liver protein digest, in addition to a diet containing 50 gm of protein and about 1200 calories, and during that time the total protein rose to 6.18

TABLE 6 *Changes Observed during Treatment with Liver Protein Digest in Patients with Severe Cirrhosis*

Case No	Liver Size*	Ascites	Serum Bilirubin		Plasma Protein		Result
			TOTAL mg/100 cc	DIRECT mg/100 cc	Albumin gm/100 cc	Globulin gm/100 cc	
15	Not palpable	+++ to +	3.08 to 2.24	0.79 to 0.66	2.5 to 2.8	3.9 to 3.0	Death in coma
16	4 to 4	++++ to ++	2.71 to 1.42	1.01 to 0.45	2.5 to 2.8	3.3 to 3.2	Moderate improvement
17	Not palpable	+++ to ++++	1.04 to 1.04	0.25 to 0.33	—	—	Death in coma
18	Not palpable	+++ to ++++	1.52 to 1.48	0.36 to 0.48	—	—	Death of hemorrhage from esophageal varices
19	Not palpable	++++ to ++++	5.92 to 3.00	2.44 to 1.16	2.1 to 1.7	4.3 to 4.1	Slight improvement

*Distance palpable below the costal margin

markedly underweight. After ten days of treatment the ulcer was almost completely healed, and the patient had gained 6 pounds.

Nitrogen balances were followed in 4 patients, in 2 of whom the liver protein digest was given to total 50 per cent of a 200-gm protein diet (2300 to 2700 calories). These two patients retained an average of 11.7 and 7.6 gm of nitrogen daily over a ten-day

period, with an albumin concentration of 3.30 gm per 100 cc although she gained only 4 pounds.

DISCUSSION

Good food, properly selected and in adequate amounts and taken by mouth, is the most effective and satisfactory method of supplying essential nutrients. Purified diets may lack some essential

TABLE 7 *Liver Protein Digest in the Treatment of Patients with Thermal Burns*

Case No	Sex	Body Surface with Third-Degree Burn %	Nutritional Status			Interval before Treatment	Duration of Treatment	Amount of Liver Protein Digest	Weight Change	Result
			On Entry	Beginning of Treatment	End of Treatment					
34	F	20	Fair	Poor	Fair	730 days	36 days	450 gm/day	+2 lb	Slow healing
36	M	46	Fair	Fair	—	4	9	94	—	Death
33	F	15	Fair	Fair	Fair	15	70	50 to 150	—1	Moderate healing
35	M	15	Good	Fair	Good	94	32	540	+6	Rapid healing
37	M	10	Good	Fair	Fair	84	37	167	0	Moderate healing

period. Another patient, who received 65 gm of protein from the liver protein digest and a basic diet containing 75 gm of animal and vegetable protein, retained an average of 8.6 gm of nitrogen daily. The last patient, an alcoholic addict, was put on a basic 25-gm protein diet for ten days, during which he was in nitrogen equilibrium. At that point, liver protein digest was added isocalorically to the diet, bringing the protein intake to 75 gm daily over the next ten-day period. This patient retained an average of 5.7 gm of nitrogen daily.

Plasma proteins were followed in 3 of the 4 cases in which nitrogen balances were determined. The plasma protein concentrations were not abnormal

as yet unknown. Thus, monkeys fed purified diets containing all the known dietary essentials fail to gain weight and develop a macrocytic anemia that is cured by liver.¹⁶ This missing component has recently proved to be the synthetic *Lactobacillus casei* factor.¹⁷ In view of this and similar investigations, it is unlikely that all the essential nutrients are known. It seems, therefore, a good practice to supply natural foods or their derivatives as sources of calories, protein and vitamins. Recently, it has become the custom for physicians to prescribe large amounts of one vitamin or a multivitamin capsule for their patients. The administration of large amounts of a single vitamin to the exclusion of others

sensitivity in any of the patients treated with the digest

Peptic Ulcer

Liver protein digest was administered to 3 patients with duodenal ulcer. In 1 of these it was used as a supplement to a soft diet and in the other 2 as the

the diarrhea was aggravated. Nevertheless, during that time, the patient gained 5 pounds in weight, and the symptoms and signs of peripheral neuritis, which had been relatively acute at onset, were markedly diminished. The other 2 patients, both with a longer history of peripheral neuritis, had gradual improvement such as one would expect with

TABLE 4 Changes Observed during Treatment with Liver Protein Digest in Patients with Mild Cirrhosis

CASE No	LIVER SIZE cm	SERUM BILIRUBIN		PLASMA PROTEIN		RESULTS
		TOTAL mg / 100 cc	DIRECT mg / 100 cc	ALBUMIN gm / 100 cc	GLOBULIN gm / 100 cc	
1	4 to 0	1.38 to 0.76	0.48 to 0.31	—	—	Marked improvement
2	6 to 0	1.14 to 0.66	0.46 to 0.19	3.70 to 4.69	2.57 to 2.57	Marked improvement
3	2 to 0	3.40 to 1.00	1.88 to 0.52	3.65 to 4.65	2.81 to 2.03	Marked improvement
4	5 to 1	4.82 to 0.64	2.35 to 0.11	3.35 to 2.79	1.76 to 3.40	Marked improvement
5	6 to 0	0.50 to 0.11	0.06 to 0.07	3.85 to 3.78	2.02 to 1.98	Marked improvement
6	4 to 0	2.70 to 1.00	1.40 to 0.35	—	—	Marked improvement
7	3 to 1	0.70 to 0.38	0.01 to 0.12	—	—	Marked improvement
8	7 to 3	1.56 to 1.14	0.59 to 0.38	—	—	Marked improvement
9	3 to 2	0.64 to 0.74	0.25 to 0.18	—	—	Moderate improvement

sole source of oral protein for three to five days. These last 2 patients are of interest in that they were admitted with marked pyloric obstruction and almost complete gastric retention. The liver protein digest was administered through a gastric tube at hourly intervals, and gastric contents were aspirated to relieve distention. This was necessary every four hours for the first twenty-four hours, but by the third or fourth day the obstruction had been completely relieved and aspirations were no longer necessary. The patients were then placed on a soft diet, and liver protein digest was given as a supplement. The weight gains in these patients were remarkable, 1 patient gaining 18 pounds in ten days,

optimum vitamin therapy. Approximately 180 gm of the liver protein digest was administered daily for thirteen and forty-eight days respectively, when the patients were discharged from the hospital.

Malnourishment

Fourteen patients exhibiting various degrees of malnutrition due to restricted food intake were studied. In 6 the restricted diet was voluntary and was usually accompanied by chronic alcoholism. The remaining patients had a variety of conditions, including bronchiectasis, Parkinson's disease, healed duodenal ulcer, hemophilia, hypernephroma and postoperative malnourishment. These patients re-

TABLE 5 Changes Observed during Treatment with Liver Protein Digest in Patients with Moderate Cirrhosis

CASE No	LIVER SIZE cm	ASCITES	SERUM BILIRUBIN		PLASMA PROTEIN		RESULT
			TOTAL mg / 100 cc	DIRECT mg / 100 cc	ALBUMIN gm / 100 cc	GLOBULIN gm / 100 cc	
10	1 to 0	++ to 0	—	—	2.6 to 2.9	3.2 to 3.7	Marked improvement
11	4 to 1	+++ to 0	2.85 to 0.82	1.54 to 0.62	2.7 to 4.2	3.2 to 3.8	Marked improvement
12	4 to 1	+++ to +	—	—	—	—	Marked improvement
13	Not palpable	+++ to +	0.66 to 0.72	0.48 to 0.18	3.5 to 3.6	3.6 to 3.2	Moderate improvement
14	10 to 2	+++ to 0	—	—	3.7 to 4.1	3.6 to 3.1	Marked improvement

and the other 10 pounds in six days. More studies are being carried out on patients with peptic ulcer. No conclusions can be drawn from this series, but the results, particularly in obstructive lesions, are hopeful and are similar to those recently reported by Co Tui² with a casein hydrolysate.

Peripheral Neuritis

The liver protein digest was given to 3 patients with peripheral neuritis associated with chronic alcoholism. In 1, a thirty-one-year-old woman with moderate diarrhea on admission, the liver protein digest had to be discontinued after five days because

ceived the liver protein digest in amounts of approximately 100 gm of protein daily for four to twenty-three days. Whenever possible, changes in body weight were observed, and in 4 patients nitrogen balance and plasma protein concentrations were followed.

No improvement was shown in 2 patients — one with a hypernephroma extending into the hepatic vein, who developed marked ascites and eventually died, and the other, a patient with Parkinsonism who presented a feeding problem and was transferred to a nursing home. Of the other patients, 2 were followed for four and five days respectively.

SUMMARY

A partial enzymatic digest of liver protein was administered as a food supplement to 65 patients. The digest contained 60 per cent protein, in addition to relatively large quantities of vitamin B complex.

The taste of the liver protein digest is somewhat disagreeable, and a laxative effect was observed in some patients.

The liver protein digest supported positive nitrogen balance or nitrogen equilibrium when given as the chief source of protein to 5 normal subjects and 4 malnourished patients.

Plasma protein regeneration was demonstrated in 1 patient with nephrosis and in 1 with uncomplicated malnutrition, as well as in several patients with cirrhosis of the liver.

The results of the treatment of 19 patients with portal cirrhosis of the liver was at least as satisfactory as those attained with other means of supplying the many nutrients that have recently been advocated for the treatment of this disease. The recovery of 5 patients with infectious hepatitis progressed satisfactorily.

The liver protein digest proved to be an adequate protein supplement for 4 of 5 patients with severe thermal burns.

The digest was given to 3 patients with peptic ulcers, 2 of whom had marked pyloric obstruction. The results in these 3 patients were excellent.

Recovery in 3 patients with alcoholic peripheral neuritis who received the liver protein digest was approximately the same as was expected from the duration and severity of the condition.

Fourteen patients with malnourishment of various causes received the liver protein digest. Marked improvement was observed in 10.

REFERENCES

- 1 Patek A. J. Jr. and Post J. Treatment of cirrhosis of liver by nutritious diet and supplements rich in vitamin B complex. *J Clin Investigation* 20 481-505 1941
- 2 Peters J. P., and Bulger, H. A. Relation of albuminuria to protein requirement in nephritis. *Arch Int. Med* 37 153-185 1926
- 3 Co-Tui F. W. Wright A. M. Mulholland, J. H. Galvin T. Barcham I., and Gerst G. R. Hyperalimentation treatment of peptic ulcer with amino acids (protein hydrolysate) and dextrin maltose. *Gastroenterology* 5:5 17 1945
- 4 Elman, R. Acute starvation following operation or injury with special reference to caloric and protein needs. *Ann Surg* 120:350-361 1944
- 5 Levenson S. M., Davidson C. S. Lund C. C., and Taylor F. H. L. Nutrition of patients with thermal burns. *Surg Gynec & Obst* 80 449-469 1945
- 6 Holman R. L., Mahoney, E. B. and Whipple, G. H. Blood plasma protein regeneration controlled by diet. I. Liver and casein as potent diet fractions. *J Exper Med* 59 251-267, 1934
- 7 Pommerenke W. T. Slavin H. B., Karber D. H., and Whipple G. H. Blood plasma protein regeneration controlled by diet. Systematic standardization of food proteins for potency in protein regeneration. Fasting and iron feeding. *J Exper Med* 61 261-282 1935
- 8 Weech, A. A. and Goettsch E. Dietary protein and regeneration of serum albumin. Potency values of egg white, beef liver and gelatin. *Bull Johns Hopkins Hosp* 64 425-433, 1939
- 9 Committee on Diagnosis and Pathology. Food and Nutritional Board, National Research Council. *Inadequate Diets and Nutritional Deficiencies in the United States. Their prevalence and significance* 56 pp. Bulletin No 107 November 1943
- 10 Rose W. C., Haines W. J., Johnson, J. E., and Warner, D. T. Further experiments on rôle of amino acids in human nutrition. *J Biol. Chem* 148 457 1945
- 11 Howe P. E. Use of sodium sulfate as globulin precipitant in determination of proteins in blood. *J Biol. Chem* 49 93-113 1921
- 12 Duca H., and Watson C. J. Quantitative determination of serum bilirubin with special reference to prompt reacting and chloroform soluble types. *J Lab & Clin. Med* 30:293-300 1945
- 13 Hanger F. M. Serological differentiation of obstructive from hepatogenous jaundice by flocculation of cephalin-cholesterol emulsions. *J Clin Investigation* 18 261-269 1939
- 14 Ley A. B., Lewis J. H. and Davidson C. S. Quantitative determination of thymol turbidity reaction of serum. *J Lab & Clin Med* (in press)
- 15 Souter A. W., and Kark, R. Quick's prothrombin time simplified by use of stable thromboplastin. *Am. J. W. Sc* 200 603-607 1940
- 16 Day P. L., Langston W. C. Darby W. J. Wahlin, J. G. and Mima, V. Nutritional cytopenia in monkeys receiving Goldberger diet. *J Exper Med* 72 463-477 1940
- 17 Wilson H. E., Saslaw S. and Doan C. A. Effect of folic acid (*Lactobacillus casei* factor) in nutritional hematopenia of monkeys. *J Lab & Clin Med* 31 631-642 1946
- 18 Morgan A. F. Effect of imbalance in "filtrate fraction" of vitamin B complex in dogs. *Science* 93 261 1941
- 19 Stare F. J. and Thorn G. W. Protein nutrition in problems of medical interest. *J A M A* 127 1120-1127, 1945
- 20 Lund C. C. and Levenson, S. M. Protein in surgery. *J A M A* 128 95-100 1945
- 21 Russakoff A. H., and Blumberg H. Choline as adjuvant to dietary therapy of cirrhosis of liver. *Ann Int Med* 21 848-862 1944
- 22 Beams A. J. Treatment of cirrhosis of liver with choline and cysteine. *J A M A* 130 190-194 1946
- 23 Cope O. J., Nathanson, I. J., Rourke M. G. and Wilson H. Metabolic observations. In Aub J. C. and others. *Management of the Coconut Grove Burns at the Massachusetts General Hospital* 171 pp. Philadelphia Lippincott 1943. Pp 137-158
- 24 Hirschfeld, J. W., Williams H. H. Abbott W. F. Heller C. G., and Pilling M. A. Significance of nitrogen loss in exudate from surface burns. *Surgery* 15 766-775 1944
- 25 Taylor F. H. L. Levenson, S. M., Davidson C. S., and Adams M. A. Abnormal nitrogen metabolism in patients with thermal burns. *New Eng J Med* 229 855-859 1943
- 26 Minot G. R., Strauss M. B., and Cobb S. "Alcoholic polyneuritis dietary deficiency as factor in its production." *New Eng J Med* 208 1244-1249, 1933
- 27 Williams, R. R., and Spies T. D. *Vitamin B (Thiamin) and Its Use in Medicine* 411 pp. New York Macmillan Company 1938

may be dangerous,¹⁸ and few multivitamin capsules can be considered to supply in optimum amounts all the nutrients falling into this class. It seems evident, therefore, that a natural product containing the known essential nutrients is the best means of supplying a diet supplement. The liver protein digest admirably meets these requirements so far as protein and the vitamin B complex are concerned. It should be emphasized, however, that the digest does not provide other vitamins or sufficient calories in itself to prevent the burning of protein for energy.

Mixtures of nutrients in various combinations and amounts have been used as diet supplements for years and have recently been re-emphasized in protein feeding.^{19, 20} In many cases they form the greater part of the food intake and thus must be planned with care to meet all the possible requirements. This is difficult for the physician without a particular interest in nutrition, especially in providing the vitamin B complex, and the liver protein digest, given with sufficient calories, vitamin C and, if necessary, the fat-soluble vitamins, therefore forms an important addition to the dietary armamentarium.

In addition to supplying nutrients, a food supplement should be palatable and without unpleasant side-effects. The bitter aftertaste of the liver protein digest is unpleasant to many patients, and in fact some took it only because they were convinced of its value. A few could or would not take the mixture at all. The laxative effect of the digest was also severe enough in some patients to require discontinuance of the mixture. Many others had an increase in the number of bowel movements a day that was not distressing, however.

That the liver protein digest will maintain nitrogen equilibrium in normal subjects when it is used as the chief source of protein is clearly demonstrated in the 5 normal persons described above. Furthermore, in 4 patients who had lost weight it was possible to maintain a strongly positive nitrogen balance. Plasma protein regeneration with a strongly positive nitrogen balance was evident in a patient with nephrosis, in whom the liver protein digest formed about half the protein intake, and in a patient with severe malnutrition.

Recent studies have emphasized the value of food intake in the treatment of portal cirrhosis of the liver. Special emphasis has been placed on protein and the vitamin B complex,¹ methionine and choline.^{21, 22} The presence of these substances makes the liver protein digest theoretically exceptionally good in the treatment of this condition. The results in the 19 patients with cirrhosis support this view. In our experience, the improvement was at least as good if not somewhat better than that with any other means of administering the food elements necessary. These results, in addition to the relative ease of administration of such a diversity of substances, make the liver protein digest extremely

useful in the specific therapy of cirrhosis of the liver.

It has been repeatedly pointed out that the nutritional requirements of patients with thermal burns are high.^{5, 23} This is especially true of protein, large amounts of which are lost from the burn surface²⁴ and in the urine as nonprotein nitrogen.²⁵ These patients are usually extremely ill and have marked anorexia so that attaining the nutritional requirements is often difficult and requires frequent changing of the dietary supplements to add variety to the food intake. In this way the liver protein digest formed a useful protein supplement in the patients studied and proved to be at least as satisfactory as the other supplements used.

Peripheral neuritis in alcoholism is generally regarded as a deficiency disease,²⁶ thiamine being specifically implicated.²⁷ Most patients with this condition have evidence of multiple dietary deficiencies so that rational therapy should be directed toward a more complete replacement therapy than with thiamine alone. The results presented above do not indicate any more beneficial effects than those afforded by other means of attaining adequate intake of nutrients, in fact, in a patient with peripheral neuritis complicated by diarrhea, the digest had to be discontinued because of increase in the latter symptom. Nevertheless, the improvement in all 3 patients with peripheral neuritis was about what one would expect from optimum dietary therapy. More than 10 mg of thiamine was supplied daily to these patients in food and liver protein digest.

The etiology of peptic ulcer remains unknown, although there is no doubt that psychologic factors play an important role. Many patients suffering from peptic ulcer improve markedly under almost any regime that offers relief from psychologic problems, as well as under local and general medical treatment. Local treatment of the ulcer is best achieved by reduction of gastric acidity through the use of buffering substances. General medical treatment includes hydration, regulation of acid-base balance and improvement of general nutrition. Obstruction of the pylorus in peptic ulcer may be due to either edema or scar formation. It is often difficult to differentiate these conditions without a therapeutic trial. In the 2 cases of ulcer discussed above complete six-hour gastric retention was shown by x-ray study before treatment. It was believed by many observers that the obstructions were due to scar formation, and we were surprised at the rapidity with which these obstructions were relieved, indicating that they had been due to edema and inflammation. The liver protein digest offers an excellent buffering agent as well as a good food and if given at frequent intervals seems to offer a satisfactory method of treatment. More studies will be necessary to determine the efficacy of this therapy in ulcer patients.

quite certain even without roentgenologic study. Hyperextension of the knee is often so marked that the lower leg is brought into contact with the thigh. The skin in front of the knee is slack and wrinkled, the patella being palpable but smaller than that of the opposite leg. Occasionally, the patella seems to be absent. The condyles of the femur and the tibial displacement are palpable, and the loss of flexion is obvious. When these findings are present, the diagnosis is established. In roentgenologic studies confirmatory evidence is offered, but it must be remembered that the joints are largely cartilaginous so that a clear picture of the relation of joint surfaces to each other cannot with certainty be obtained. In these cases, however, the angle and displacement between axes of the tibia and femur will be noted.

Early, conservative, manipulation of the knee is the most efficient method of therapy. In the majority of cases in which conservative treatment was instituted soon after birth, excellent anatomic and functional results were obtained. The longer the treatment is delayed, the more difficult the therapeutic procedures required and the less favorable the results. At a later period, surgical intervention is often necessary, and regardless of the treatment the reports show poor end results when compared with those in patients treated early.

The type of conservative method used differs depending on the surgeon. Essentially, the procedure consists of early reduction and maintenance of the reduced position followed by a gradual increase in flexion. When the patient begins to walk, a lateral knee brace or knee cage may be necessary.^{54, 55}

CASE REPORT*

A female infant, the head presenting, was delivered normally after 8 hours of labor. The birth weight was 7 pounds, 14 ounces. There was no family history of congenital lesions. Seven days after birth, except for the findings limited to the right leg, physical examination revealed a normal infant. The right leg was hyperextended. The skin over the knee was loose and markedly wrinkled. The tibia was anterior to the femoral condyles, the distal end of the femur projecting posteriorly to the proximal portion of the tibia. The patella, located above the knee joint, was smaller than that of the left leg. There was laxity of the collateral ligaments.

On reflex action, the right lower leg was hyperextended on the femur to about 90 to 110°. From this point, the lower leg could be painlessly hyperextended to the thigh. Flexion could not be obtained unless traction was first applied to reduce the dislocation, when the leg could be straightened. Clicking of the knee joint was noted as the tibia passed over the distal end of the femur. The left leg was normal.

Treatment, which was started immediately, consisted of traction on the femur to reduce the dislocation. A malleable aluminum posterior splint was applied to maintain the position of the leg in 180° extension. On the 2nd day, the splint was removed and flexion was increased, heat and massage being applied to the hamstrings and the quadriceps muscle. This procedure was repeated daily, allowing an increase in passive motion of flexion and extension to 180°. The attained position of flexion was maintained and increased by the use of the aluminum splint. Within 2 weeks, flexion was complete, but hyperextension was not allowed. Within 4 weeks, the splint was removed, and the knee did not dislocate.

Although it was not deemed necessary to keep the splint applied, it was used 4 weeks longer, after which it was removed. During the manipulations no anesthesia was necessary.

On weight bearing, the leg appeared normal. After 3 years, examination of the right leg revealed no abnormal findings, and the child was able to run, play and jump as well as any other child her age.

SUMMARY

An etiologic classification of dislocations of the knee is presented. The diagnostic features are discussed. The incidence of the condition in relation to sex, types and familial tendencies is described. The comparative results of various treatments are mentioned. A detailed case presentation is given.

In the treatment of congenital dislocations of the knee, the end results obtained are dependent on the etiologic factor involved and the time at which treatment is instituted. In patients with traumatic developmental lesions, excluding those with secondary malposition, early conservative treatment, even without anesthesia, results in normal anatomic and functional knee joints. In the presence of multiple lesions, the final outcome depends on the seriousness of the other congenital anomalies present. The necessary surgical procedures often used in the treatment of this lesion cannot compare with the results of early conservative therapy.

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REFERENCES

- McFarland B. L. Congenital dislocation of knee. *J Bone & Joint Surg* 11:281-285 1929.
- Hussen M. K. Multiple congenital dislocation. *J Bone & Joint Surg* 20:488 1938.
- Spiers H. W. Congenital luxation of knee. *J Bone & Joint Surg* 9:469-475 1927.
- Wentworth E. T. Gradual reduction of congenital anteriorly dislocated knees. *J Bone & Joint Surg* 10:585 1928.
- Hamada G. Congenital dislocation of knees treated by manipulation. *Brit M J* 2:141 1950.
- Grossman J. Congenital dislocation of both knees. *M J & Rec* 125:189 1927.
- Griswold A. S. Congenital dislocation of knee joint. case report. *J Bone & Joint Surg* 9:628 1927.
- Boorstein S. W. Congenital genu recurvatum. *M J & Rec* 124:541 1926.
- Idem. Congenital backward dislocation of knee. *Am J Dis Child* 38:107-111 1929.
- Kopits E. Beiträge zur Pathologie und Therapie der angeborenen Kniegelenksluxationen. *Arch f Ortop* 23:593-603 1925.
- Baldwin C. H. Congenital dislocation of knee joint. *J Bone & Joint Surg* 8:822 1926.
- Prince L. D. Congenital genu recurvatum. *Surg Gynec & Obst* 24:714-725 1917.
- Szenes A. Pseudoluxation im Kniegelenk und Luxation des Fusses im Talocruralgelenk nach hinten als Geburtsverletzung des Neugeborenen. *Arch f Gynäk* 129:482-503 1927.
- Rochol H. H. Über Knie-Luxationen. *Arch f Ortop* 24:589-596 1927.
- Jagerink T. A. Genu recurvatum congenitum. *Nederl tijdschr v geneesk* 2:476 1927.
- Bohm M. Infantile deformities of knee and hip. *J Bone & Joint Surg* 15:574-578 1933.
- Middleton D. S. Pathology of congenital genu recurvatum. *Brit J Surg* 22:696-702 1935.
- Scougall S. Comparative anatomy of knee joint in relation to congenital anomalies. *M J Australia* 1:691-694 1930.
- Sorrel E. and LeGrand-Lambing M. Tripe malformation congenitale des membres inferieurs. *Bull Soc de pediat de Paris* 30:169-171 1932.
- Giannelli A. Sulla lussazione congenita bilaterale della rotula. *Gier di med mil* 81:483-487 1933.
- Keizer D. P. R. A propos d'un cas de luxation congenita e antérieure bilaterale du genou. *Voormissio* 21:359-362 1935.
- Marchese E. Sopra un caso di genu recurvatum congenitum e cetera di funicolo. *Clin orth* 36:629-635 1934.

*Reported through the courtesy of Dr. Daniel J. McSweeney.

CONGENITAL DISLOCATION OF THE KNEE*

Report of a Case

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ALTHOUGH congenital dislocation is extremely rare, it is the most frequent congenital deformity of the knee. In recent years the occurrence and the treatment of this lesion have received considerable attention,¹⁻³⁶ but to date an etiologic grouping has not been presented. It is the purpose of this paper to formulate an etiologic classification of congenital dislocations of the knee, to review the various cases reported to determine the incidence in relation to hereditary tendencies, sex and types of dislocations, to discuss the numerous treatments prescribed and to present the case of a patient treated by simple conservative manipulation and early physiotherapy and followed for a period of three years.

Many theories have been advanced regarding the cause of congenital dislocations of the knee^{16, 17, 26, 33, 36-50}. Drehmann,³⁸ Mayer³⁷ and others^{6, 39, 51, 52} believe that malpositions in utero are the primary causative factors, genu recurvatum and true dislocations being different only in severity. Hussein² and Kopits¹⁰ consider mesenchymal defects the cause of multiple and universal abnormalities. McFarland¹ and others^{12, 15, 28} believe the lesion to be due either to a primary defect or to malposition in utero. Magnus⁴⁰ and others^{41-43, 45, 47-50} regard an intrauterine fetal illness as the cause.

In a determination of the etiologic factors involved, intrauterine or intrinsic causes and extrauterine or extrinsic causes must be considered. The former refer to dislocations arising from maternal or fetal intrauterine disturbances, and the latter to factors other than those related to maternal or fetal conditions, such as the necessary manipulations performed by the obstetrician during the process of delivery. The intrauterine or intrinsic causes can be divided into primary mesenchymal defects and traumatic developmental defects, the latter may be subdivided into developmental malposition in utero occurring during the developmental processes, secondary malposition in utero superimposed on a previously existing mesenchymal defect and malposition assumed during the actual process of delivery.

The severity of the condition seen at birth and the prognosis are dependent on the causative factor or factors involved. In the patients with primary defects, the lesions are usually multiple and there-

fore more difficult to treat, and the prognosis is necessarily based on the outlook for the other existing anomalies. In the traumatic group the lesions are usually single or bilateral, except for dislocations superimposed on a pre-existing mesenchymal defect, in which group multiple lesions are found. That this type can occur is shown by McFarland,¹ who reports a case in which x-ray findings before delivery revealed a fetus in utero with one leg flexed and the other hyperextended and in which other deformities were found at birth. The dislocations seen in the traumatic group when not complicated by other congenital deformities yield excellent results with simple conservative manipulation, provided treatment is instituted early.

A review of the literature reveals that neither familial nor hereditary factors truly influence the incidence of congenital dislocations of the knee. In addition, an attempt was made to determine whether or not acute maternal illnesses caused predisposition to the development of these congenital defects. It was noted that there was no relation between acute infectious diseases occurring in the mother during pregnancy and the development of this anomaly in the newborn. Of 212 patients whose cases were reviewed, a family history of a similar defect or some other congenital deformity was reported in only 7. In 174 cases the occurrence of acute maternal illnesses was denied. No mention of virus infections in the mother was made.

Against the belief of Muskat⁴¹ and others^{12, 28, 45} who state that these dislocations occur twice as often in girls, it was found that of the 212 cases of congenital knee dislocations, 101 appeared in males and 111 in females. It was also shown that the types of lesions were distributed about equally between the sexes. The types of dislocation included 155 cases of single dislocations and 57 of multiple deformities. Of the 155 patients in whom the knee was the only deformity noted, 95 showed unilateral and 60 bilateral dislocations. Of the 57 patients with multiple deformities, 31 presented unilateral and 26 bilateral dislocations of the knee. Kopits¹⁰ observed that among 2393 cases of congenital deformity there were only 11 of dislocation of the knee as compared with 923 of congenital dislocation of the hip.

In congenital dislocations of the knees, the findings described by the various investigators^{3, 6, 7, 9, 11, 21, 33} are essentially the same, and although the lesions are sometimes difficult to classify, the diagnosis is

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plastics methyl methacrylate (Lucite and Plexiglas), "nylon," a generic term applied to a group of polyamides, vinyl resins (Vinylite), polyethylene (Polythene), and cellulose nitrate (celluloid) and regenerated cellulose (cellophane). It should be stated that on rare occasions plastic materials have been selected for use in the body because of their ability to set up a moderately intense reaction and to stimulate the formation of scar tissue. This subject is discussed below at greater length. Each of the plastics mentioned above is considered in a separate section of this report.

A brief account should first be given of the chemical and physical properties of plastics in general. A plastic is a solid material that contains as an essential ingredient an organic substance of large molecular weight and that, at some stage in its manufacture or in its conversion into end products, is capable of being shaped by flow.¹ The Plastics Materials Manufacturers Association has defined plastics as synthetic organic materials that, through application of pressure or heat, or both, may be fashioned into almost any desirable shape, varying from solids capable of fabrication by turning on a lathe to liquids that can be sprayed. Industrial plastics have been divided by Kline² into four categories: synthetic resins, natural resins, cellulose derivatives, and protein substances. It is not proposed to discuss the natural resins or the protein substances, since they are composed of complex chemical structures that are often not purified and have not been found suitable for use in tissues. Cellulose derivatives are primarily of historical interest, except for the isolated use of materials to stimulate scar tissue.

Interest is centered chiefly around the synthetic resins, many of which have simple chemical structures. The chemist has been able to synthesize materials that have the hardness of stone, the transparency of glass, the flexibility of rubber or the insulating ability of mica. In general, organic plastics are resistant to atmospheric and chemical corrosion and possess high structural strength, light weight, low heat conductivity and good electric-insulation value. The synthetic resins found most satisfactory for use in surgery are as a whole composed of long-chained polymers of simple monomeric structure. These have been converted into polymers by the influence of catalysts or by the effect of light, heat, oxygen or extreme pressure.

Synthetic resins are either thermosetting or thermoplastic. Thermosetting plastics are made extremely hard by heating, and their value in industry in general depends on this quality; this group has not been used in surgical procedures. Thermoplastic products are fusible, soften when heated and become hard again when cold.³ The extremes of temperature variation in the animal or human body are not sufficient to alter the physical properties of any thermoplastic materials signifi-

cantly. It is therefore with the thermoplastic synthetic resins that this paper is chiefly concerned, and the subsequent discussion centers around this group. Some of the plastics found useful in surgery are hard, and are employed because of that property, such a material is methyl methacrylate. Others, like polyethylene, are used because they are pliable and soft and are suitable for surgical application because they attain this softness through their own structure and not by the addition of plasticizers.

Most thermoplastic linear polymers of high molecular weight are hard, brittle solids at room temperature. On heating they soften and gradually become more flexible and plastic. The flexibility at room temperatures can be increased by the addition of materials of relatively low molecular weight, called "plasticizers." A great variety of plastic materials have been made available to industry by the use of such plasticizers.⁴ Plasticization is essentially a separation of chain molecules by the plasticizer molecules converting hard plastics with long-chained molecules into pliable plastics with shorter molecules. Camphor, tricresyl-phosphate, glycerol and many other chemicals have been utilized as plasticizers. Plasticizers usually remain within the plastic material, and most of them have been found to be irritating to human and animal tissues.⁵ It seems safest, therefore, to exclude from surgical usage all plastics that contain plasticizers, unless in the future varieties can be found that are not tissue irritants. This, of course, greatly narrows the field of potential plastic substances available to the surgeon.

METHYL METHACRYLATE

This long-chained polymer has been used more extensively and with greater success in both experimental and clinical surgery than any other synthetic resin. It is produced commercially under the trade names of "Lucite" and "Plexiglas" but is generally known as acrylic, particularly in the field of dentistry. In England it is frequently called "Perspex."

Methyl methacrylate is obtained by the polymerization of derivatives of acrylic acid. Under the influence of heat, light and such oxygen-yielding substances as hydrogen peroxide, the esters of acrylic acid and methacrylic acid polymerize through various stages to form methyl methacrylate.⁶ This substance is considered to exist in chains of various lengths, formed by the linking together of the original monomeric molecules.

Methyl methacrylate can be cast in the form of sheets, rods or tubes, or it can be cast in a mold to any form desired. It has many advantageous physical properties. It is hard and tough, has high tensile strength, and is light, with a specific gravity of 1.18 to 1.20. It is chemically inert and stable, has negligible water absorption, is transparent, and has a high velocity resistance.^{7, 8} It is nonporous, and its surface is impervious to the ingrowth of bacteria, hence, it is easily sterilized. It has been found to

- 23 Guillemin, A. Luxation du genou suivant un axe vertical *Bull et mêm Soc nat de chir* 55 608-612 1929
- 24 Salasachs, G. L. Congenital genu recurvatum *Rev méd de Barcelona* 25 122-135 1936
- 25 Menciére, J. L. Un cas de luxation congénitale de la rotule en dehors avec rotation de 90° de l'axe des deux os de jambe sur l'axe du fémur *Rev d'orthop* 24 239 243, 1937
- 26 Martin du Pan C. Le genu recurvatum congénital *Rev méd de la Suisse Rom* 57 604-607 1937
- 27 Pintos C M., and Rivarola J E. Genu recurvatum congénito *Arch argent de pediat* 8 1145 1150, 1937
- 28 Kaiser, R. Über kongenitale Kniegelenkluxationen *Acta orthop Scandinav* 6 1-20, 1935
- 29 Frejka, B. Treatment of congenital dislocation of knee joint *Bratisl lekár listy* 17 466-473, 1937
- 30 Wahl, F. A. Beitrag zum Genu recurvatum congenitum *Zentralbl f Gynäk* 54 3265 3268, 1930
- 31 Wittek A. Zur Pathologie des Kniegelenkes *Deutsche Zeitschr f Chir* 225 308-320, 1930
- 32 Winter, H. Über die angeborene Luxation des Kniegelenkes nach vorn und ihre Operation *Arch f orthop* 28 94-99, 1930
- 33 Henrard, E. Zur Ätiologie und Prognose des Genu recurvatum congenitum beim Neugeborenen *Monatsschr f Geburtsh u Gynäk* 80 317, 1928
- 34 Richter, H. Die angeborene Beugekontraktur und die angeborene hintere Verrenkung des Kniegelenkes *Beitr z. klin Chir* 146 111-123, 1929
- 35 Goldstein, D., and Tichonow, W. Ein seltener Fall von kongenitalem beiderseitigen Genu recurvatum *Arch f orthop u Unfall Chir* 34 48 55, 1933
- 36 Köhler, A. Mitteilung eines Falles angeborener Luxationen der unteren Extremitäten *Zeitschr f orthop Chir* 58 401-415, 1933
- 37 Mayer, L. Congenital anterior subluxation of knee description of new specimen, summary of pathology of deformity and discussion of its treatment. *Am J Orthop Surg* 10 411-437, 1913
- 38 Drehmann, G. Deformitäten nach Gelenkentzündungen im frühesten Säuglingsalter *Zeitschr f orthop Chir* 14 712-720 1905
- 39 Bacilieri, L. Über kongenitale Luxationen im Kniegelenk. *Arch f Orthop* 3 213 234, 1905
- 40 Magnus F. Über totale congenitale Luxation der Kniegelenke bei drei Geschwistern *Deutsche Zeitschr f Chir* 78.555 573, 1903
- 41 Muskat G. Die congenitalen Luxationen im Kniegelenk. *Arch f klin Chir* 54 852-884 1897
- 42 Perthes, G. Zur Pathologie und Therapie der angeborenen Luxation des Kniegelenkes. *Zeitschr f orthop Chir* 14 629-635, 1903
- 43 Youmans, J. Intra uterine dislocation of knee joint. *Boston M & S J* 63 249, 1860
- 44 Richardson, W. L., and Porter, C. B. Two cases of congenital dislocation of knee joint. *Boston M & S J* 93 321 324 1875
- 45 Potel, G. Le genu recurvatum congénital. *Echo méd du Nord* 1: 372-376, 1897
- 46 Roberts, J. B. Congenital anterior dislocation of tibia treated by arthrotomy. *Ann. Surg* 34 286-288, 1901
- 47 Phocas, G. Genu recurvatum congénital ou luxation congénitale de tibia en avant *Rev d'orthop* 2 50-64, 1891
- 48 Guéniot, C. Déformation et raccourcissement considérables de la jambe chez une petite fille saillie angulaire énorme du tibia en avant. *Bull et mêm Soc de chir de Paris* 6.557 561, 1880
- 49 Hibon, L. De la luxation congénitale du tibia en avant avec rétrécissement de la jambe sur la cuisse. *Pacte thèse.* 98 pp 1881
- 50 Redard P. *Traité pratique de chirurgie orthopédique* 1047 pp Paris Doin, 1892
- 51 Grunewald E. A. Die kongenitalen Luxationen des Kniegelenkes. *Freib* 8 31, 1914
- 52 Lovett J. Case of congenital subluxation of knee joint. *Med res Bergen* 47 22 27, 1930.
- 53 Evans, E. L. Multiple congenital dislocations. *Proc Roy Soc Med (Surg Sect)* 14 26, 1921
- 54 Cochrane W. A. *Orthopaedic Surgery* 528 pp New York William Wood and Company, 1926.
- 55 Whitman, R. *A Treatise on Orthopaedic Surgery* 993 pp Philadelphia Lea and Febiger 1923

MEDICAL PROGRESS

SYNTHETIC PLASTIC MATERIALS IN SURGERY*

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THE last thirty years have witnessed a tremendous growth in the plastics industry, and a great variety of new plastic materials have been developed. In the field of medicine they have been used chiefly in the production of surgical and medical diagnostic and therapeutic instruments. A limited application of plastic materials buried within the human body has been found, however, and it is with this use of plastics that this progress report is concerned. No attempt is made to review related medical fields, such as dentistry.

The selection of plastic materials for use in the body has been in large part fortuitous. Without previous laboratory trial, various plastics possessing certain desirable physical properties were employed sporadically in operative procedures. Some of these were well tolerated in the body, others were quite severe irritants to tissues. In more recent years, an increasing number of papers dealing with experi-

mental surgery using plastics appeared. One plastic material, methyl methacrylate, was found to be well tolerated in the mouth by dentists, and was subsequently utilized by surgeons.

✓ Certain general criteria should be met in the selection of any substance to be buried in human tissue. The material should be nonabsorbable and not modified by tissue fluids, chemically inert, free from excitation of early or late tissue reaction, non-epileptogenic when buried in brain tissue and non-carcinogenic. There are rare exceptions, but in general any solid plastic to be used in normal human tissue should satisfy these criteria.

Industry has developed literally thousands of varieties of plastic materials, and at first sight the wealth of information available is overwhelming. A careful selection of materials that fulfill specific surgical needs quickly limits the number of these substances that require investigation. Animal experimentation should be carried out to determine the reaction of individual materials in tissue before these substances are used in the surgery of human beings.

Sufficient experimentation has been done to warrant discussion of the following well known

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ack in small skull defects by the use of preformed acrylic plates of various sizes, which he put in place at the time of the primary operation. He used these only in patients without neurologic deficit and in those in whom the dura was intact. He reported 48 cases in which this technic was employed.

Blum²⁶ refers to another method of speeding up the process of polymerization of methyl methacrylate. This is done by the addition of a special catalyst, whose composition is not given, to the methyl methacrylate "dough." The material is exposed to ultraviolet rays, and the process of polymerization requires only fifteen minutes. Blum stated that the substance did not produce dural reaction or changes in the underlying brain tissue. The same method is mentioned in a later publication²⁷, in addition, reference is made to the fact that methyl methacrylate sheets can easily be molded at 130°C. If rapidly cooled, they will retain the shape into which they have been molded and can be boiled or autoclaved. These methods will contribute significantly to shortening the operating time in cranioplasty with methyl methacrylate.

Acrylic has been used in several other areas of the body to replace the metallic alloy, vitallium. It is considered by some to be ideal for arthroplasty, particularly in arthritis of the hip. Harmon²⁸⁻³¹ has described the use of acrylic in hip arthroplasties in several reports and is enthusiastic about the results. In his last report he had done hip operations with acrylic cups in 16 cases. The results were excellent in 62 per cent, good in 19 per cent and poor in 19 per cent. He believed that the poor results in 2 of 3 cases were due to error in selection of cases. The relief of pain in arthritis of the hip was reported as dramatic in many of the cases. Burman and Abrahamson¹⁵ employed acrylic in arthroplasty of the hip in 1 case and of the finger in 2, with good results.

Methyl methacrylate has also been used in plastic surgery for sculpturally molded implants in facial deformities, as described by Brown³² and by Penhale.¹¹ It has been implanted in the scrotum in patients who had had previous orchidectomies.³³ In addition to being light and well tolerated in the scrotum, the implants provided considerable cosmetic improvement and psychologic comfort. After a year in place, they showed no evidence of unusual tissue reaction to gross palpation.

Dennis¹⁶ implanted specially formed methyl methacrylate tubes into cavities of the long bones of patients with chronic osteomyelitis. He reported that the tubes stayed in place twelve to fifteen months and were well tolerated, and that satisfactory healing of the chronic infections took place as a result of this procedure.

In the field of experimental medicine, Sohler, Lothrop and Forbes³⁴ first made use of Lucite windows screwed into the skulls of animals with

the acrylic in contact with the brain. These were employed to observe the circulation of blood over the cortex for a period of many weeks without the occurrence of infection. An excellent elaboration of this technic has been described by Sheldon et al.³⁵ who were able to fashion a transparent Lucite calvarium covering the entire top of a monkey's head. This was held in place with screws. Several of the coverings were left in place for many months. This type of experiment offers an exceptional opportunity for observing the surface of the brain under essentially normal conditions of intracranial pressure and cerebral circulation. Owing to the lack of reaction to methyl methacrylate, the scalp edges around the base of the plate healed rapidly and showed no infection.

Merendino and Litow⁷ fashioned gastrostomy tubes that could be maintained in position in experimental animals for several months. They suggested the use of this material for gastrostomies in human beings but did not report any such cases.

A little known property of methyl methacrylate is that described by Hirschboeck,³⁶ who found that tubes and small containers made of methacrylate possessed an anticoagulant power that he believed to be due to the pronounced water-repelling property of the surface of the material. The coagulation time in Lucite tubes is approximately twice as long as that in glass. The application of this property to the use of acrylic in vascular surgery suggests itself. Brief reference to this possibility is made by Mustard,³⁷ although he refers to no specific type of plastic material.

Hufnagel³⁸ performed a series of anastomoses of the thoracic aorta in 18 dogs after resecting 1 to 3 cm of the aorta. He used tubes of methyl methacrylate 4 cm in length and 1.0 to 1.3 cm in diameter, with walls 1 mm thick, to bridge the gap. Particular care was taken to polish the inner wall of the tubes so that there were no rough areas or irregularities. These tubes were tied in place with two braided-silk sutures at each end of the tube. Six dogs died of hemorrhage seven to ten days after operation, owing to cutting through of the suture, but this was obviated in later experiments by the use of a coarser braided-silk suture that gave multiple point fixation. The striking result of these experiments was that thrombosis did not occur in a single animal either in the tube or in the aorta. Some of the animals lived as long as six months in excellent health.

DeBakey and Simeone,³⁹ in a discussion of the treatment of arterial injuries in battle wounds of 2471 soldiers in World War II, mention the occasional use of plastic tubes in vascular anastomosis. They found records that this method had been used in 14 cases, but the type of plastic employed was not mentioned. The results, which were not recorded in individual cases, were discouraging in general. The authors believed that blood was

be nonabsorbable in human tissues and unchanged when buried in them. It retains its form and does not begin to soften until heated above 150°F. In repeated reliable experimental and clinical studies, it has been shown to be well tolerated in both animal and human tissues.

Mackenzie, Sharpless and Millard⁹ performed animal experiments to compare the reaction of tissues to vitallium, ticonium and acrylic. Histologic studies were done at intervals, and photomicrographs are published in the paper. Acrylic was found to cause no inflammation whatever. A thin, fibrous, tissue membrane that became increasingly dense over a six months' period formed around the material. Vitallium and acrylic were tolerated about equally well in the short series of experiments, ticonium was less satisfactory.

Beck et al.¹⁰ buried disks of acrylic in the skulls of rabbits. They used 16 animals, in half of which they removed the dura under the disk, and sacrificed the animals at intervals up to seven months. The plastic was well tolerated, being surrounded by a thin, fibrous, tissue capsule, to which it was not adherent. In some animals in which the underlying dura had been removed there were mild adhesions between the thin fibrous capsule and the leptomeninges, but the brain was normal in all. The photomicrographs showed no evidence of foreign-body reaction to the acrylic, which was considered to be well tolerated.

Woolf and Walker¹¹ also presented photomicrographs of acrylic buried in tissues over a prolonged period in which the plates were encapsulated by a thin layer of connective tissue. Acrylic did not incite any foreign-body reaction even in the presence of wound infection. This has been borne out clinically by Elkins and Cameron,¹² who reported 70 cases of cranioplasty in combat wounds of the head. They found no complications attributable to acrylic, some of their plates had been in place two years. In one case in which infection occurred, the plate was not removed, and the wound subsequently healed satisfactorily. There are other scattered reports of the effect of acrylic on tissues. Penhale¹³ buried acrylic in the subcutaneous tissues of monkeys for seven days. Reproductions of the histologic sections showing the slight reaction that occurred were published. The reaction was much less than that caused by cartilage or ivory. Penhale reported several patients who had had implants in place for the correction of facial deformities for over three years without complications.

Burman¹⁴ and Burman and Abrahamson¹⁵ describe methyl methacrylate as reactionless, gross and microscopical studies of the subcutaneous tissue of rabbits after implantation of the material showed no reaction after eighty days. They performed three arthroplasties using this material with satisfactory results. Dennis¹⁶ observed that Lucite caused no significant reaction in the muscle of a dog after

thirty days. Davis⁸ states that the acrylic used in protecting helmets for airmen causes no unfavorable reaction if accidentally driven into tissues.

Spealman and his associates¹⁷ studied the toxicity of methacrylates by oral, intraperitoneal and subcutaneous administration and by inhalation. The monomeric form was mildly irritating, but in the final polymeric form the acrylic showed no irritation and no tendency to sensitize animals. Implantation in subcutaneous tissues of mice provoked no tumor growth.

The medical literature on this particular synthetic resin is more extensive than that on any other. The material has been adequately tested and found suitable for a variety of surgical uses, some of which have also been reviewed by commercial publications.¹⁸

Methyl methacrylate is admirably suited for the repair of defects of the skull. As suggested by Woolf and Walker,¹¹ nonmetallic alloplastic grafts for skull defects should fulfill certain criteria: they should be inert and not modified by tissue juices, they should not be epileptogenic or carcinogenic, they should be sufficiently rigid to maintain contour, they should offer little or no resistance to x-rays, and they should cause little or no immediate or late tissue reaction. Methyl methacrylate meets these standards adequately, and a number of reports of its use in cranioplasty attest its value.

The article of Elkins and Cameron¹² mentioned above presents the largest reported series in which acrylic was employed. Woolf and Walker¹¹ considered it one of the most satisfactory materials for cranioplasty. Gurdjian, Webster and Brown,¹⁹ Lambros,²⁰ Woodhall,²¹ Kahn²² and Kerr²³ describe methyl methacrylate as a satisfactory material for cranioplasty. Small and Graham²⁴ recently reported the use of methyl methacrylate for the closure of skull defects in 25 patients. They had only one failure, in a patient in whom there had been a previously infected subdural hematoma. Their paper, profusely illustrated, describes in great detail the technic of forming and inserting the plates.

The acrylic plates are made by the impression technic, which requires either a two-stage procedure or a delay of about one and a half to four hours during an operation while the plate is being formed. Its use is somewhat more complicated than that of tantalum, but because it is not opaque to x-rays and can be fashioned somewhat more satisfactorily to obliterate dead spaces in tissue, it is probably superior to that material for cranioplasty in most cases. Acrylic is considered easier to use than vitallium. Since it is widely employed in dental laboratories, the co-operation of a dentist in any large hospital facilitates its use.

One of the strongest objections to methyl methacrylate for cranioplasty is the time required to form the plates. Shoreston²⁵ has circumvented this draw-

proved Burman believed that nylon used in this way caused a certain amount of serous fluid to collect around it, a property that he regarded as desirable in this operation.

Weiss and Taylor⁵⁰ employed multiple fine strands of nylon to aid in bridging nerve gaps in experimental animals. By an ingenious technic worked out by them, the gap between the nerve ends is bridged by the nylon fibers and filled with solid blood clot. This is covered by collagen or some other sheath to prevent the ingrowth of scar tissue. Weiss and Taylor considered that the nylon fibers, by producing linear areas of liquefaction through the blood clot, provide orienting pathways across the gap for the regenerating nerve fibers and thus prevent whorling and neuroma formation. Their method has met with success in smaller animals, rats and cats.

VINYL RESINS

The use of plastics referred to as "Vinylite" is occasionally reported. This is one of the trade names employed to describe a variety of manufactured products varying from polyvinyl alcohol to a polymerized mixture of vinyl chloride and vinyl acetate. These substances are often mixed with a plasticizer to give them pliability, and an almost limitless number of materials can be compounded under the term "Vinylite." Few reports of the actual use of vinyl compounds within the body have appeared. It would be only a coincidence if two investigators used the same chemical compound, since this product is a highly variable one.

Bailey and Ford⁵¹ report that a Vinylite compound buried in the abdominal wall of guinea pigs caused only slight tissue reaction. MacQuigg⁵² used a vinyl chloride polymer in the form of a tube for prolonged intramuscular injections. Such tubes were left in place up to four days without apparent reaction. Narat and Cipolla⁵³ found that a vinyl derivative called "Tygon" inactivated penicillin when kept in contact with it for twenty-four to seventy-two hours. There was a 38 per cent deactivation of the penicillin in seventy-two hours, and the same inactivation was observed with rubber tubing. It was suggested that either this material not be used for the administration of penicillin or that the dosage given through it be correspondingly increased. Whether shorter periods of contact between the tubing and the penicillin deactivated the latter was not recorded.

The vinyl compounds have found extensive use in the formation of prostheses in plastic surgery^{54, 55} and in forming protective layers over the skin, as around ileostomies and colostomies.⁵⁶ There is a reasonably large group of papers on this phase of the subject, but since this is not strictly related to the use of plastics within the body, no effort has been made to review this literature.

(To be concluded)

REFERENCES

1. *Plastics Educational Booklet* 14 pp. American Association of School Administrators November 1 1945
2. Kline, G. M. *Organic Plastics* 27 pp. U. S. Department of Commerce National Bureau of Standards 1936
3. Reinhardt, F. W., and Kline, G. M. *Plastics organic. M. Physics* Pp 1101-1105 1944
4. *Plasticizers. Plastics Catalogue* 300 pp. New York Plastics Catalogue Corporation 1944
5. Mead, D. J., Tichenor, R. L., and Fuoss, R. M. Electrical properties of solids. XII. Plasticized polyvinyl chloride. *J. Am. Chem. Soc.* 64 283-291 1942
6. *Acrylic resins. Plastics Catalogue* 300 pp. New York Plastics Catalogue Corporation 1944 P. 85
7. Merendino, K. A. and Litow, S. S. "Lucite" gastrostomy tube for pouch dogs and possibilities for application in man. *Surgery* 15 526-531 1944
8. Davis, L. Helmet for protection against craniocerebral injuries. *Surg., Gynec. & Obst.* 79 89-91 1944
9. Mackenzie, C. M., Sharpless, D. H., and Millard, P. Tissue reactions to vitallium and acrylic implants. *American Med.* 44 277-283 1945
10. Beck, D. J. K., Russell, D. S., Small, J. M., and Graham, M. P. Implantation of acrylic resin discs in rabbits' skulls. *Brit. J. Surg.* 33 83-86 1945
11. Woolf, J. I. and Walker, A. E. Cranioplasty: collective review. *Internat. Abstr. Surg.* 81 1-23 1945
12. Elkins, C. W., and Cameron, J. E. Cranioplasty with acrylic plates. *J. Neurosurg.* 3 199-205 1946
13. Penhale, K. W. Acrylic resin as implant for correction of facial deformities. *Arch. Surg.* 50 233-239 1945
14. Burman, M. Plastic materials in medicine: preliminary report on use of lucite and nylon fabrics in orthopedic surgery. *Am. J. Surg.* 62 124 1943
15. Burman, M., and Abrahamson, R. H. Use of plastics in reconstructive surgery. Lucite in arthroplasty: tissue tolerance for lucite as use as interposition mold in arthroplasty of hip and of phalangeal joints. *Mil. Surgeon* 93 405-414, 1943
16. Dennis, C. Prolonged dependent drainage with "lucite" drains in treatment of chronic osteomyelitis. *Surgery* 13 900-910 1943
17. Speilman, C. R., Main, R. J., Haas, H. B., and Larson, P. S. Monomeric methyl methacrylate: studies on toxicity. *Indust. Med.* 14 292 1945
18. *Plastics in Medicine and Surgery* 9 pp. E. I. du Pont de Nemours and Company Incorporated July 1946
19. Gurdjian, E. S., Webster, J. E., and Brown, J. C. Impression technique for reconstruction of large skull defects. *Surgery* 14 876-881 1943
20. Lambros, V. S. Repair of large cranial defect: report of case in which large cranial defect was repaired by graft from ilium. *Arch. Surg.* 46 575-580 1943
21. Woodhall, B. Cranioplasty. In Bancroft, F. R., and Pilcher, C. *Surgical Treatment of the Nervous System* 534 pp. Philadelphia J. B. Lippincott & Company 1946
22. Kahn, E. A. Contrast media in lesions of cerebral hemisphere. *Proc. Roy. Soc. Med.* 36 403-405, 1943
23. Kerr, A. S. Use of acrylic resin plates for repair of skull defects. *J. Neurol. & Psychiat.* 6 158 1943
24. Small, J. M., and Graham, M. P. Acrylic resin for closure of skull defects: preliminary report. *Brit. J. Surg.* 33 105-113 1945
25. Shoreston, J. Primary skull closure with acrylic plates. *Proc. Congress of C. M. F. Army Surgeons* Rome February 12-19 1945 P. 123
26. Blum, G. Experimental observations of use of absorbable and non absorbable plastics in bone surgery. *Proc. Roy. Soc. Med.* 38 169-171 1945
27. Blaine, G. Uses of plastics in surgery. *Lancet* 2 525-528 1946.
28. Harmon, P. H. Arthroplasty of hip with lucite cups. *Guthrie Clin. Bull.* 11 9-16 1941
29. *Idem.* Methacrylate resins in surgery. *Mod. Plastics* 20 56, 1942.
30. *Idem.* Results during first year following hip arthroplasty with non-metallic foreign body cups of methacrylate plastic: pathogenesis and operative technique. *Guthrie Clin. Bull.* 11 124-130 1942
31. *Idem.* Arthroplasty of hip for osteoarthritis utilizing foreign-body cups of plastic. *Surg., Gynec. & Obst.* 76 347-365, 1943
32. Brown, A. M. Sculpturally molded synthetic implants in plastic surgery. *Arch. Otolaryng.* 39 179-183 1944
33. McCrea, L. E. Lucite: new synthetic material suitable for testicular prosthesis. *Urol. & Cutan. Rev.* 42 723-725 1938
34. Sohler, T. P., Loshrop, G. N., and Forbes, H. S. Pial circulation of normal non-anesthetized animals. I. Description of method of observation. *J. Pharmacol. & Exper. Therap.* 71 325-330 1941
35. Shelden, C. H., Pudenz, R. H., Restarski, J. S., and Craig, W. M. Lucite calvarium method for direct observation of brain: surgical and lucite processing techniques. *J. Neurosurg.* 1 67-75 1944
36. Hirschboeck, J. S. Delayed blood coagulation in methyl methacrylate (boilable "lucite") vessels. *Proc. Soc. Exper. Biol. & Med.* 47 311 1941
37. Mustard, W. T. Technic of immediate restoration of vascular continuity after arterial wounds. *Ann. Surg.* 124 46-59 1946
38. Hufnagel, C. A. Unpublished data
39. DeBakey, M. E., and Simeone, F. A. Battle injuries of arteries in World War II: analysis of 2471 cases. *Ann. Surg.* 123 534-579 1946
40. Edds, M. V. Prevention of nerve regeneration and neuroma formation by caps of synthetic resin. *J. Neurosurg.* 2 507-509 1945
41. Kline, G. M. Chemist's wonderland. *Chem. & Eng. News* 22 890-899 1944

likelier to clot rapidly in plastic tubes than in vein grafts for vascular anastomosis, although the use of plastic tubes, if satisfactory, would be a simpler technical method

Edds⁴⁰ published a description of a method of preventing neuroma formation in severed peripheral nerves by coating the proximal end of the nerve with a 10 per cent solution of methyl methacrylate in acetone. This was successful in the nerves of rats up to a diameter of 1.5 mm, but it was not applied extensively to larger nerves. It was suggested that to make the procedure effective in larger nerves, the epineurium must be retracted from the end of the nerve before the acetone and methacrylate are applied.

NYLON

"Nylon" is a generic term applied to a large family of related chemical compounds and not to a single pure product. This large group of chemical compounds consists of polymeric amides whose molecular structure is made up of alternate groups of NH-CO and CO-NH with a variable number of interposed methylene groups.⁴¹ Chemically, they resemble natural proteins. Nylons are used widely as filaments to fabricate a variety of products, such as stockings and parachutes. They are thermoplastic, and although they soften at a higher temperature than most thermoplastic substances, they can be readily extruded or molded into various forms. It is in the form of a filament that nylon plastics have been utilized in surgery, specifically in the form of suture material.

Since the term "nylon" refers to a large group of chemically related but structurally different compounds, it is obvious that to discuss the use of nylon in surgery, one should know exactly what chemical compound is used in each product so labeled. This is difficult because, as in some other plastics discussed below, commercial secrets prevent general knowledge of the detailed composition of individual products. In practice, nylon in the form of filaments of various sizes is supplied to medical supply houses, which take the responsibility of dispensing the material in desirable forms. They also take the responsibility of furnishing to those who use the material a nylon filament that by previous experimental study has been found suitable. Whether one medical supply house dispenses nylon sutures identical with those dispensed by any other supply house is not known. The same criticism might be leveled against catgut, silk or cotton, whose exact structures surgeons do not know but which are used because the same product has been found satisfactory year after year.

Nylon, using the term as applied to surgical suture material, is odorless, tasteless and resistant to most chemicals, and withstands repeated autoclaving without weakening of its innate toughness and elasticity. It does not deteriorate significantly with

age, is not absorbed when buried in human or animal tissues and is extremely strong. A strand of nylon compared to a strand of silk of the same size has been found by Nichols and Diack⁴² to be stronger, more elastic and more resistant to moisture absorption.

Nylon can be supplied as either a monofilament or a braided suture. Melick,⁴³ Haxton⁴⁴ and Arnes⁴⁵ have reported studies comparing the two forms of suture. It seems generally agreed that the monofilament causes slightly less tissue reaction than the braided form of multifilament material, but is harder to handle and more difficult to tie in knots that will not slip. In point of fact, the criticism of slipping of knots tied with nylon has been directed against the braided form as well as the monofilament. Unless sutures are tied carefully, particularly with the larger sizes of nylon, there seems to be more tendency to slip than when silk sutures are used.

Clinical trials of nylon as a suture material have appeared in the literature in reports by Stonham,⁴⁶ Haxton⁴⁴ and Burman.⁴⁷ All these authors have recommended nylon as superior to silk or any other suture material for general use.

Experimentally, adequate studies of nylon as a suture material have been made by several investigators. Melick⁴³ reports that in the early stages of healing there is more reaction around nylon multifilament sutures than around silk but that the final result is the same, neither suture material showing any significant tissue reaction compared to that caused by catgut. Arnes⁴⁵ observes that nylon causes less reaction than silk and that in infected wounds, leukocytes are found around silk longer than around nylon. Nichols and Diack⁴² state that the reaction to silk and nylon is about the same, but they favor the latter because of its greater tensile strength.

It is not known whether these various workers, who obtained the material with which they experimented from different supply houses, employed the same chemical product, but their results agree so closely that one can only conclude that there is minimal tissue reaction to the nylon sutures generally used. In an extensive study of wound healing, Localio, Casale and Hinton^{47, 48} tested the strength of wounds in rats sutured with catgut, cotton, steel-alloy wire, silk and nylon. They found nylon equal to cotton, steel wire, and silk, and better than catgut. Their figures indicated there was slightly more rapid firm union with nylon than with any of the other sutures, but the rate of healing with all the non-absorbable sutures tested did not vary enough to be statistically significant.

Burman⁴⁹ has reported a series of 4 cases of arthroplasty of the small joints of the finger with so-called "parachute nylon" as an interposition membrane. Only 1 of the cases was reported in detail, and the patient was considered greatly im-

an amount from 250 to 1300 cc daily. The urinary output ranged between 750 and 250 cc daily. Retrograde pyelogram on the twelfth hospital day showed nothing unusual. The urine was sterile on admission, but later a moderate number of and abundant colonies of colon bacilli were grown respectively from the right and left ureteral specimens. On the fifteenth day a bromsulfalein test showed 22 per cent retention of the dye after forty-five minutes. With the constant vomiting the patient's condition grew worse. A questionable pericardial friction rub was heard. The temperature ranged between 99 and 100°F during the entire admission. The patient was found dead on the twentieth hospital day.

DIFFERENTIAL DIAGNOSIS

DR EARLE M. CHAPMAN: May I see the x-ray films?

DR RICHARD SCHATZKI: So far as the kidneys are concerned I should say that in the intravenous pyelogram they are a little enlarged. Some of the films show a small amount of dye in the kidney pelvis. The surprising thing to me about the intravenous pyelogram is that there is any dye visible with specific gravities of the urine of only 1.008 and 1.011. The retrograde pyelogram shows that the kidneys are normal in size and shape. The area of calcification mentioned is on the left side and shifts around inside the abdomen. The chest shows a small area of either atelectasis or scar in the posterior lower aspect of the left lower lobe, with a small amount of fluid in this area. The few stomach films that we have show a deformity that is by no means characteristic, and I thought that it would be wise to look at the x-ray report made at that time and found that the examination had been unsatisfactory. The examiner could see the patient only in the horizontal position. The deformity involves the antrum as well as the immediate postpyloric region. I cannot see any tumor mass in the stomach, nor can I be sure whether or not there is an ulcer present, but my impression, along with that of the fluoroscopist, is that no ulcer is visible.

DR CHAPMAN: I think that you will agree with me that this is, indeed, a case in which it is going to be difficult to come out with a diagnosis that covers the syndrome. There are one or two questions that I think fair to have answered from the record. It seems to me that there must have been some comment during a nine-week illness whether this woman's bowels moved, especially while she was in the hospital.

DR TRACY B. MALLORY: They did.

DR CHAPMAN: And I should like to take a quick look at the electrocardiographic tracings. The ST segments in all leads were sagging, and the T waves in Leads 1 and 3 were inverted. I am looking also at the P waves to see if they were inverted, since the right and left arm electrodes may have been mixed; it could have been a technical error.

We can discuss first the more probable diagnoses in this patient and then those that are speculative and put them together to try to explain this woman's death in renal failure, with a low nonprotein nitrogen. It is stated in the record that she appeared far sicker than the temperature or the nonprotein nitrogen indicated. Indeed she was. She died without any indication of the true diagnosis by the laboratory and other investigative procedures.

The patient had had rheumatic fever, that brings up the question, Did she have rheumatic heart disease and attendant disorders? I believe that there is not enough evidence in this record to establish rheumatic heart disease or heart failure in the final illness as having been responsible for death. At the age of thirty-seven the patient had a hysterectomy—in other words, injury to the pelvis of a surgical nature. X-ray study revealed an area of old calcification, although its duration was not known, lying apparently on the left side in the region of the left kidney. That suggests an old healed tuberculous lesion of many years' duration.

We then come to the illness of nine weeks' duration characterized by weakness, edema of the lower extremities, severe nausea and finally almost constant vomiting. The gall bladder had been removed for these symptoms, but I believe that this was an unnecessary operation—it was done in good faith but did not relieve the patient. It was following this that she had the first episode that I believe was the first clue to what was wrong. I interpret these signs and the sudden onset of pain in the lower left chest as having been due to a large pulmonary infarction. Indeed, we know that the first pulmonary infarct usually slithers into the left lower lobe, it has been pointed out by Allen, Linton and Donaldson¹ that 70 per cent are found in the left lower lobe. In support of this diagnosis is the persistence of the physical signs despite the treatment with penicillin, which was given on the basis, I suppose, of infection. In further support, I think that the electrocardiographic changes were similar to those that are seen in the presence of pulmonary infarction. They were not entirely typical because in acute pulmonary infarction changes in the S waves are described. This tracing is abnormal but not diagnostic of any particular type of heart disease, although it does suggest obstruction of the pulmonary artery.

The final consideration is the renal failure. What type of renal failure was this? Why did the patient die in this peculiar manner? I think that the presence of large kidneys demonstrated by Dr Schatzki excludes glomerulonephritis or any other type of chronic process. I cannot believe that this was amyloid disease because no chronic infectious process was demonstrated. Immediately, one wonders if at operation done outside this hospital some form of sulfonamide was dusted into the wound, whether this was a sulfathiazole reaction in the kidney, and whether these were toxic kidneys.

- 42 Nichols, H M and Diack, A W Experimental study of nylon as suture material preliminary report *West J Surg* 48 42-46, 1940
- 43 Melick, D W Nylon suture *Ann Surg* 115 475, 1942
- 44 Haxton, H A Nylon for buried sutures *Brit M J* 1 12, 1945
- 45 Ames, L J Experimental studies with synthetic fiber (nylon) as buried suture. *Surgery* 9 51 60 1941
- 46 Stonham, F V Nylon *Indian M Gaz* 77 283, 1942
- 47 Localio, S A, Casale, W, and Hinton, J W Wound healing — experimental and statistical study. III Experimental observations *Surg, Gynec & Obst* 77 243 249, 1943
- 48 *Idem* Wound healing — experimental and statistical study. IV Results *Surg, Gynec & Obst* 77 376-388, 1943
- 49 Burman, M Nylon fabric arthroplasty of the carpo-metacarpal joint of thumb *Bull Hosp Joint Dis* 4 74 78, 1943
- 50 Weiss, P, and Taylor, A C Guides for nerve regeneration across gaps *J Neurosurg* 3 375 389, 1946
- 51 Bailey, O T, and Ford, R Fibrinogen plastics tissue reactions induced by a series of fibrinogen plastics implanted in abdominal wall of guinea pigs *Arch Path* 42 535 542, 1946
- 52 MacQuigg, R E New techniques for parenteral fluid and drug administration muscular intubation *Surgery* 18 592 595 1945
- 53 Narat, J K, and Cipolla, A E Inactivation of penicillin by taking preliminary report *Am J Surg* 71 667 1946
- 54 Editorial Polyvinyl chloride for prostheses *Brit M J* 1 563, 1946
- 55 Gordin, M M, Bau, R G, and Kevan, J E, Jr. Extra-oral facial prosthesis elastic vinyl plastic method *U S Nav M Bull* 64 644-650, 1944
- 56 Presman, D New method of skin protection for ileostomies and colostomies *Surgery* 13 322, 1943

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

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CASE 33101

PRESENTATION OF CASE

A forty-seven-year-old housewife entered the hospital complaining of pain along the left costal margin

Nine weeks before admission the patient had consulted a physician because of fatigue, swelling of the feet and ankles, vomiting and epigastric pain. The pain was intermittent, usually occurring after fatty or fried foods or cabbage had been eaten. It was sharp, lasted a few minutes and was most marked at the left costal margin, occasionally radiating medially into the epigastrium. It was aggravated by inspiration and by the attacks of vomiting, which usually occurred once a day about thirty minutes after a meal. The patient was given digitalis and sent home to bed. During the following week the ankle swelling subsided, but the other symptoms persisted. Seven weeks before admission a fibrous, contracted gall bladder containing a single stone was removed at another hospital. Ten days later the patient felt a sharp pain in the left lower chest and developed dyspnea and physical and x-ray signs of consolidation of the left lower lobe of the lung. The temperature and pulse were elevated. The symptoms persisted despite penicillin injections. Seventeen days before entering the Massachusetts General Hospital, she went home against advice. At home she felt feverish and anorexic, but noted no chills, petechiae or edema.

At the age of fourteen years an attack of fever and joint pain had kept the patient in bed about four weeks. At the age of thirty-seven she underwent a hysterectomy.

Physical examination revealed the patient to be pale and apparently acutely ill. The tongue was red and smooth, and the skin rough and dry. The apical beat was regular at a rate of 110. A Grade I systolic and a questionable presystolic murmur were

heard at the apex. There were dullness, decreased breath sounds and decreased tactile fremitus at the base of the left lung posteriorly. The entire right side of the abdomen felt resistant. At the upper pole of the vertical scar in the right upper quadrant there was a draining sinus. An old healed scar occupied the midline above the symphysis. There was slight pitting edema of both ankles.

The temperature was 99.6°F, the pulse 105, and the respirations 26. The blood pressure was 140 systolic, 70 diastolic.

Examination of the blood disclosed a red-cell count of 2,400,000, with a hemoglobin of 10 gm per 100 cc, and a white-cell count of 21,000, with 82 per cent neutrophils and 16 per cent lymphocytes. The specific gravity of the urine varied between 1.008 and 1.011. The urine gave a +++ to ++++ test for albumin, and the sediment contained innumerable granular casts but no cells. The blood nonprotein nitrogen was 41, the phosphorus 5.5 and the sugar 88 mg per 100 cc, the total protein was 6 gm per 100 cc with an albumin of 2.45 and a globulin of 3.55 gm, and the carbon dioxide 24.2 milliequiv per liter. An electrocardiogram showed a rate of 138, with a PR interval of 0.18 second, slurred QRS complexes, sagging ST segments in Leads 1, 2 and 3, diphasic T waves in Leads 2, CF₁ and CF₄, inverted T waves in Leads 1, 3 and CF₁ and sagging ST segments in Leads CF₁, CF₄ and CF₆. On x-ray examination the heart was somewhat globular, and the cardiothoracic ratio was 12.5:26.0. On the left the posterior portion of the diaphragm was elevated, and there was a hazy area of increased density in the left side of the chest posteriorly, with a few linear areas of increased density extending upward obliquely from the diaphragm. A barium meal demonstrated slight deformity of the antrum and prepyloric area and enlargement and deformity of the duodenal cap without ulceration. In the intravenous pyelogram the kidneys appeared large. The dye was poorly excreted, and only on the right were faintly outlined calyces visible. There were several calcified nodules opposite the third lumbar vertebra.

In the hospital the patient was lethargic and almost constantly nauseated, appearing far sicker than the temperature or the nonprotein nitrogen warranted. All food was vomited. A duodenal tube was inserted, but vomiting continued, varying

nary emboli. There was a localized peritonitis in the lesser peritoneal cavity, but we found nothing intrinsically wrong with the stomach or duodenum. The posterior surfaces of both the stomach and the duodenum were bathed in pus from this localized peritoneal abscess. The kidneys, as Dr Schatzki predicted, were enlarged. Microscopically they showed a rather extensive fatty vacuolization of all the proximal convoluted tubules—a lesion that is consistent with the severe albuminuria that this patient had. The liver also showed rather marked fatty vacuolization, particularly at the periphery of the lobules—the type of vacuolization that is seen in patients with starvation, it might be attributed to the vomiting for a period of several weeks.

DR. CHAPMAN: Were these changes consistent with amyloid disease in the kidneys? I mentioned that as possibly occurring secondary to an infection.

DR. MALLORY: There was no amyloidosis. Anatomically, we must call this lesion lipid nephrosis, although the clinical picture was somewhat unusual.

DR. CHAPMAN: How about the heart?

DR. MALLORY: It was entirely normal, weighing 260 gm. There was a calcified tuberculoma of the spleen.

REFERENCES

1. Allen A. W., Linton, R. R. and Donaldson G. A. Thrombosis and embolism: review of 202 patients treated by femoral vein interruption. *Am. Surg.* 118:723-740, 1943.
2. Chapman E. M. and Anderson R. G. Aids in physical diagnosis: signs over lower left lung caused chiefly by cardiac enlargement. *Ann. Int. Med.* 23:35-40, 1945.

CASE 33102

PRESENTATION OF CASE

A twenty-eight-year-old Italian housewife was admitted to the hospital because of easy fatigability.

The patient stated that she had felt tired for three weeks. This fatigability was associated with some dizziness, occasional faintness and nausea and vomiting. She had had no cough, the menstrual flow had diminished recently, and she had missed one period. She had had no other vaginal bleeding.

Because of rheumatoid arthritis she had been admitted to this hospital seven years previously and had subsequently been followed in the Out Patient Department. Four years before the previous admission an appendectomy and a removal of an ovarian cyst had been performed in another hospital.

Physical examination revealed a thin, pale woman with spindling of most of the fingers and thickening of the tissues around the right knee. The blood pressure was 105 systolic, 45 diastolic, and there was a Grade I systolic murmur at the apex.

Examination of the blood disclosed a red-cell count of 2,000,000, with a hemoglobin of 5.8 gm and a hematocrit of 20, and a white-cell count of 2800, with a normal differential. The urine was normal. Several stools were guaiac positive. A gastric analysis revealed no free hydrochloric acid either

before or after histamine, with 5 units of combined acid in each specimen. Plain films of the chest and abdomen were normal.

Two days after admission the white-cell count rose to 5500, without change in the red-cell count. A gastrointestinal series and barium enema were negative except for slight deformity of the stomach opposite the incisura, somewhat suggestive of an ulcer on the posterior wall. A blood count done shortly after admission revealed 4.5 per cent reticulocytes. Liver-extract therapy was instituted two weeks after admission, and three days later the reticulocytes had risen to 6.6 per cent. On the fourth and fifth days, however, they had fallen to 4 and 3 per cent respectively. The red-cell count rose slowly, and about three weeks after admission it had reached 3,200,000, with a hemoglobin of 9.5 gm. Because of the deformity of the stomach visible on the x-ray film, a gastroscopic examination was done about two weeks after admission, revealing normal peristaltic waves and a normal pylorus. Throughout the body of the stomach, from just distal to the angulus almost to the cardiac orifice, involving the lesser curvature, posterior wall and greater curvature, the rugae were unusually thick and tortuous and presented a definitely rigid appearance, with some areas of reddening and some mucosal hemorrhage. These folds did not flatten by air inflation. Along the greater curvature and posterior wall the mucosa had a verrucous appearance. The anterior wall appeared essentially normal except for reddening. There was no blood in the stomach, and no ulceration or erosion.

Approximately a month after admission an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. BERNARD JACOBSON: We are told that this young woman had had definite rheumatoid arthritis at least seven years previously and that when admitted to the hospital she had deformities consistent with long-standing rheumatoid arthritis. From this point on, however, I shall give no further thought to the rheumatic condition, I do not believe that it was related to the present disease. We are not told whether she noticed melena. This is interesting but does not rule out a history of bleeding before admission. Of course, the symptoms of dizziness, faintness and easy fatigability are common to many diseases. In this case we can readily ascribe them to the nonspecific effects of anemia in general. We are told that the patient had missed one menstrual period. We are not told anything about the results of a pelvic examination. In view of this I shall assume that the pelvic examination was essentially negative and that the patient was not pregnant. Any severe anemia can temporarily produce amenorrhea. At the time of admission the blood pressure was 105 systolic, 45 diastolic—a rather low pressure that is consistent with the evidence of anemia.

A more probable explanation and one that seems to fit is that this woman had extensive thromboses in the venous channels leading up into the abdomen, finally going past the left renal vein, which is the lower tributary, and finally involving the right renal orifice. What supports this extremely rare diagnosis? She had renal failure, with large kidneys, anemia, fixation of the specific gravity, the presence of a large amount of albumin, granular casts, a high blood phosphorus and a high nonprotein nitrogen — I assume that the nonprotein nitrogen rose later on.

DR MALLORY It subsequently went to 54 mg per 100 cc.

DR CHAPMAN. The record states that the patient was vomiting and excreting between 750 and 250 cc of urine. We know that a fall in the urinary output below 500 cc is not compatible with long life. In fact, when the output falls below 500 cc a day few people can survive longer than ten days. At the end a pericardial friction rub developed, which is typical of patients dying in uremia. Along with this a test of liver function showed 22 per cent retention of the dye. My interpretation of this test is that there was an extensive toxic liver injury from venous thrombosis.

All through the record it states that the patient was vomiting, and an attempt was made to diagnose some disease of the gastrointestinal tract, either ulcer or obstruction, and yet apparently she did not have either. One clinical sign was pointed out to me by Dr Schatzki years ago — namely, that in patients who have severe nausea, along with vomiting, one should look for the primary disease outside the digestive tract. I think that that may have been true in this case. The patient had severe nausea and vomited continuously, and yet all the studies failed to reveal disease in the digestive tract and she did not have obstruction because the bowels moved while she was in the hospital. But what was the source of the nausea?

There is one other point that I should refer to — namely, the signs over the left lower lobe, which I attributed to pulmonary infarct.² The record states that there were dullness, decreased breath sounds and decreased tactile fremitus at the left base, these signs would also fit with a process causing occlusion of the bronchus — in particular, carcinoma. There could have been cancer within the abdomen, either primary or secondary to this lesion, but I think that that is an unlikely diagnosis and mention it only in passing.

In conclusion, I believe that this patient had had rheumatic fever — but not rheumatic heart disease — and no evidence of congestive heart failure. She had had a previous operation on the pelvis. She had calcification in the abdomen suggesting old tuberculous lesions and finally an illness with swelling of the legs, nausea and vomiting that led to death within nine weeks and during which the gall bladder, which I believe was not the cause of the ill-

ness, was removed. The only way I can explain the whole picture is by extensive venous thrombosis leading higher and higher, reaching the level of the tributaries of the renal veins and thus giving the picture of a terminal renal failure.

DR SCHATZKI I may have given the wrong impression about the deformity near the pylorus. I do not know what it is from the film, but I think that there is something definitely wrong there and it may have been produced by ulceration, although no ulcer is demonstrable now.

DR CHAPMAN I interpret the changes as probably having been due to manipulation in that area during the gall-bladder operation.

DR SCHATZKI If that is true the reaction is the most unusual one that I have seen.

DR CHAPMAN There are no signs of obstruction?

DR SCHATZKI Not on the film, and the x-ray report does not mention it.

DR CHAPMAN That was a point I tried to clear up.

MR JAMES H AUSTIN With obstruction of the inferior vena cava, would you not expect the red-cell count to be higher, and how do you explain the bromsulfalein test that is recorded?

DR CHAPMAN I do not believe that the patient had independent liver disease. That test was late in the course. She died of renal failure, and that was part of the general toxic picture.

DR LEWIS W KANE Could the x-ray film be interpreted as showing a lesion in the pancreas?

DR SCHATZKI I do not believe so. Offhand, I should say that the lesion was most probably due to a former ulcer.

CLINICAL DIAGNOSES

Chronic nephritis
Uremia

DR CHAPMAN'S DIAGNOSES

Injury from pelvic operation
Calcified tuberculous nodes left abdomen
Extensive venous thromboses ascending vena cava
Pulmonary infarction left lower lobe
Renal failure from venous obstruction

ANATOMICAL DIAGNOSES

Subdiaphragmatic and subhepatic abscess, secondary to cholecystectomy
Acute lipoid nephrosis
Fatty vacuolization of liver
Healed tuberculosis of spleen

PATHOLOGICAL DISCUSSION

DR MALLORY The trouble was not above the diaphragm, as Dr Chapman suggested on the basis of pulmonary infarcts, but beneath it. There was a large subdiaphragmatic abscess, and the only thing we found in the pleural cavity was fairly dense pleural fibrosis at the base. There were no pulmo-

the likeliest form of tumor, if it was a tumor. The preoperative diagnosis of lymphoma is almost impossible to make either by x-ray study or gastroscopy. I have made it correctly in one case in which the pathologist on the gross appearance did not believe that lymphoma was present, but the microscopic sections proved it to be lymphoma. I was probably lucky because I have been wrong since then.

DR TRACY B MALLORY: Dr Ropes, have you any comment?

DR MARIAN W ROPES: We followed this patient for a good many years, and so far as the arthritis was concerned she was doing well. The anemia came on rapidly over a period of several months. We are still entirely unable to explain the anemia. She apparently had a spontaneous remission before treatment was started and the blood picture returned to a fairly normal level. We all decided that there was probably no intrinsic disease in the stomach. The guaiac tests on the stools were only slightly positive at the time when iron therapy was being given. Whether there was major bleeding from the stomach was a question, we thought that there was none.

A PHYSICIAN: I should like to ask Dr Benedict if he would expect to visualize the crater-like fleck by gastroscopy if the lesion was on the posterior wall of the stomach.

DR BENEDICT: I should, but I did not.

CLINICAL DIAGNOSIS

'Malignant lymphoma of stomach'

DR JACOBSON'S DIAGNOSES

Simple anemia due to gastric bleeding
Malignant tumor of stomach
Rheumatoid arthritis

ANATOMICAL DIAGNOSIS

Chronic pancreatitis, with extension to wall of stomach

PATHOLOGICAL DISCUSSION

DR MALLORY: I do not know whether the operative findings or the pathological report is going to be entirely satisfying in this case. There was no tumor in the stomach. When the patient was explored the posterior wall and lesser curvature of the stomach seemed thick and densely adherent to the pancreas. Frozen section at the time of operation showed no tumor, and that fact was later confirmed by the final sections. There was a severe, extensive chronic pancreatitis, with marked adhesions to the stomach wall, but I was unable to make a diagnosis of gastritis. The stomach of any adult person, of course, always shows histologically some degree of inflammation. It has often been spoken of as physiologic gastritis. If this later becomes exaggerated in character, such as that frequently seen in association with ulcer, a picture results that the

gastroscopist describes as hypertrophic gastritis. In this case I do not believe that the inflammatory process was beyond the normal limits. Also, there was no suggestion of atrophic gastritis, the glands were well formed and contained normal numbers of chief and parietal cells. From the microscopic appearance I see no reason why the stomach was not secreting normal gastric juice.

DR BENEDICT: Some years ago Dr Mallory and I* checked up the histologic and gastroscopic findings in resected stomachs and found that we agreed fairly well regarding the presence of gastritis and the type. I think that this case, because of the severe pancreatitis, could throw off the gastroscopist and the roentgenologist. Do you agree, Dr Schatzki?

DR SCHATZKI: Yes.

DR MALLORY: I think that the deformity in the stomach was due to marked thickening of the external layers of the wall secondary to the adhesions of the pancreas.

DR JACOBSON: Is it possible to explain both the x-ray picture and the gastroscopic picture by edema?

DR MALLORY: It is difficult for us to judge edema in a resected specimen. It could, I am sure, disappear under some conditions. It could be produced by the surgeon's clamps on the stomach at operation. That is an unreliable observation on our part.

DR BENEDICT: There was an interval of two or three weeks between operation and gastroscopy. Do you regard that as important?

DR MALLORY: Considerable grades of acute gastritis can disappear rapidly. That is always a possibility.

DR JACOBSON: What do you think was the cause of the anemia?

DR MALLORY: I have no better guess than anyone else.

DR JACOBSON: I suggest that this patient be followed from the point of view of later development of pernicious anemia or atrophic gastritis. Achylia at the age of twenty-eight is not frequent and should be looked on as a basis for pernicious anemia, benign polyp or carcinoma.

DR BENEDICT: Do you think that it is the achylia gastrica or the gastric atrophy that leads to carcinoma? It is my belief that gastric atrophy leads to carcinoma—that gastric carcinoma does not develop in a healthy mucosa.

DR JACOBSON: This mucosa may not be healthy five years from now. Most people who eventually develop pernicious anemia are probably born with achylia gastrica.

DR BENEDICT: And atrophic gastric mucosa?

DR JACOBSON: I do not know.

DR BENEDICT: What about that, Dr Mallory?

DR MALLORY: I do not know how far back in youth one could see it. We do not often see atrophic gastritis in young persons.

*Benedict E B., and Mallory T B. Correlation of gastroscopic and pathological findings in gastritis. *Surg Gynec Obstet* 76:129-135, 1943.

The same thing holds true for the Grade I systolic blow at the apex. From the description of the blood counts it is obvious that this was a normocytic, normochromic anemia. We are told that the initial white-cell count was 2100, with a normal differential. We are further told that two days later the white-cell count rose to 5500. I rather discount the rise. I prefer to say that the white-cell count on admission was 2800 and two days later was found to be 5500. Accepting the statement that the differential count was normal and that there were no significant changes in the platelets or in the morphologic structure of the red cells, I think that we are forced to call this a nonspecific, simple type of anemia. We can fairly well rule out leukemia, although not completely. We can also rule out thrombocytopenia.

The roentgenologist's suggestion of an ulcer on the posterior wall of the stomach is important. It brings to mind a patient whom I followed some years ago with frank classic Addisonian pernicious anemia. He had no symptoms during four or five years of maintenance treatment, and then developed digestive symptoms that led to gastrointestinal studies, the report of the x-ray series was similar to that in the case under discussion, with the suggestion of an old healed ulcer. I am sorry that I did not evaluate the interpretation properly at that time. Instead of advising the patient to come to the hospital immediately I dillydallied, and three or four months later he presented himself with an inoperable adenocarcinoma. The fallacy of my reasoning, I hope, will not be repeated again, a patient with pernicious anemia and a patient with a long-standing achylia gastrica should never be given a diagnosis of ulcer. Something else should be suspected.

In the case under discussion, in view of the roentgenologic findings, we must definitely look for something other than ulcer in the patient's stomach. Apparently the service was of the same opinion.

Before liver was given the reticulocyte percentage was 4.5, which is definitely above normal. In view of the other findings I shall ascribe that to recent mild or moderate hemorrhage. Since we are told nothing about jaundice or yellow scleras, I assume that this was not a hemolytic anemia with a high reticulocyte count. The fact that a slight increase in reticulocytes occurred a few days after liver extract had been given has no significance. There is nothing in the abstract to suggest liver-deficiency anemia.

We are told that three weeks after admission the red-cell count was 3,200,000, with a proportional hemoglobin. This rise was undoubtedly consistent with the possibility that acute hemorrhage from the stomach had ceased and that a normal regenerative process was going on. Several years ago an interesting series of articles by a man named Schiødt*

in Copenhagen pointed out that a rise of the hemoglobin and the red-cell count in regeneration from bleeding peptic ulcer is similar to the elevation following the administration of liver extract in pernicious anemia and to that in hypochromic anemia after the administration of iron. In other words, the physiologic capacity of the bone marrow for regeneration is fairly uniform, and one can expect a person with normal bone marrow who stops bleeding to regenerate the blood as rapidly as a patient with pernicious anemia after liver extract.

Gastroscopic examination showed an area of submucosal hemorrhage. So far as I can see, this was a diffuse infiltrating lesion in the submucosa. It was entirely different from the atrophic, thin mucosa of pernicious anemia. There was nothing in the history to suggest alcoholic gastritis or other cause of severe hypertrophic gastritis.

Again assuming that the blood serologic findings were negative, we can probably dismiss syphilis of the stomach. We are therefore faced with a tumor of the stomach. In view of the extensive appearance of the gastroscopic findings I believe that this was not a benign but a malignant tumor of the stomach. The age—twenty-eight years—is not against the finding of such a tumor. The type of anemia, a simple normocytic normochromic anemia, is perfectly compatible with it. So far as the nature of the tumor is concerned I do not believe that it is in the province of anyone but the pathologist to tell. Lymphosarcoma is a good possibility in a woman of this age, if the tumor was an infiltrating carcinoma. Even leiomyosarcoma is possible. I shall therefore rest with the diagnoses of simple anemia due to hemorrhage from the stomach, malignant tumor of the stomach and old rheumatoid arthritis.

DR RICHARD SCHATZKI. The remark in the record about the x-ray findings may have given Dr. Jacobson the wrong impression about the actual appearance of the stomach. This patient's stomach at times looked perfectly normal, and, as this film demonstrates, at other times we thought that there was definite thickening of the mucosa in the region of the angle of the stomach. In this area of thickening there was something that was suggestive of ulcer. I was the examiner, and I was not too satisfied because the thickening disappeared easily—at times it was present, and at others it was not. I finally said that it was suggestive of ulcer. We thought that there was definitely something wrong with the stomach, and it was the X-ray Department that asked Dr. Benedict to do the gastroscopy.

DR EDWARD B. BENEDICT. The edema of the submucosa and the hemorrhage certainly meant acute gastritis to me, and the verrucous appearance of the mucosa meant chronic gastritis. The fact that the rugae were large and did not disappear with air inflation as they usually do suggested the possibility of lymphoma in a person as young as this—a diffuse process. I considered lymphoma

*Schiødt, E. Observations on blood regeneration in man. I. Rise in erythrocytes in patients with hematemesis or melena from peptic ulcer. *Am. J. Med. Sc.* 193 313-327 1937.

Controls shared with the fully treated group the experience of attendance at the clinic and of irradiation with the longer ultraviolet rays, for which no therapeutic effects have been claimed. Half the treated controls received in addition a maintenance dose of vitamin D.

Volunteers were allocated to the treated groups by random sampling. A comparison of the records of the groups treated with complete and long ultraviolet rays showed that the persons in the former did not differ significantly from those in the latter in respect to sickness and to the reported duration of colds. There was no evidence of a vitamin D deficiency in either group. Some subjects stated that their health had been better during the period of attendance in the clinic, but there was no evidence that this was due to the short ultraviolet rays, since the numbers were about equally distributed in the two treated groups.

The comparisons between the treated and untreated groups were not quite so clean cut probably because those in the latter could not be selected at random. The study showed that the treated group of clerical and factory workers fared no better than the untreated group in respect to absenteeism due to sickness. In respect to colds, there was actually a significant advantage to the untreated subjects. Both groups of treated miners, those receiving and those not receiving the shorter ultraviolet rays, had a significant advantage over the untreated controls in respect to sickness and total absences. Evidence, however, was given to show that the previous health of this untreated group had not been so good as that of the treated group in the previous year.

On the whole the results of the study may be interpreted as indicating that the general application of ultraviolet irradiation has none of the "tonic" effects that have been attributed to it. From this point of view, the use of artificial sunlight may be considered only as a sort of modern version of sun worship.

Dr. Colebrook's report, in addition to being a clear and careful presentation of this particular study, can also serve as a model for large-scale controlled therapeutic experiments. The methods employed in the study are presented in great detail and are critically analyzed, as are the data and the results. It should be borne in mind, however, that this study

was not concerned directly with the bactericidal action of ultraviolet light. That property, which requires ultraviolet rays of different wave lengths than those used for antirachitic irradiation, has been used in attempts to eliminate cross infections and bacterial contamination of surgical wounds. An evaluation of such uses for ultraviolet irradiation requires entirely different techniques.

NATIONAL EMERGENCY MEDICAL CARE

QUESTIONNAIRES are now being sent by the Committee on National Emergency Service of the American Medical Association to approximately 5000 physicians, selected at random, who remained in civilian practice during the war. Following a study of the replies that are received, it is expected that sound conclusions can be drawn regarding the medical care that the civilian population received during that period. Furthermore, it is hoped that intelligent opinions concerning the inadequacies that arose and how they could have been avoided will be expressed.

In view of the recent rapid advances in scientific warfare, as well as in scientific medicine, the House of Delegates of the American Medical Association, at its meeting in December, 1945, recognized that information concerning how the medical profession can best serve the military and civilian populations in the event of another national emergency must be made generally available, and the appointment of the Committee on Military Medical Service, whose name was eventually changed to the Committee on National Emergency Medical Service, was accordingly authorized. During December of last year questionnaires were forwarded to more than 50,000 former medical officers, requesting information regarding their experiences while in military service. The response was excellent, and these replies are now being analyzed and studied. The results of this study combined with those arising from an analysis of the replies to the present questionnaire should permit the drafting of recommendations that would be of inestimable value to the people of this country if another emergency should arise in the near future.

Since the present questionnaires are being sent to only a small percentage of the physicians who

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ARTIFICIAL SUNLIGHT TREATMENT IN INDUSTRY

EVER since Finsen in Denmark and Rollier in Switzerland popularized the use of natural and artificial sunlight in the treatment of nonpulmonary tuberculosis, tremendous interest in the possible general helpful effects of this form of treatment has been manifested both by the medical profession and by the general public. This interest increased still more after it was demonstrated that exposure of the skin to ultraviolet rays was effective in preventing infantile rickets and when this effect was shown to be due to the conversion of the ergosterol present in the skin into vitamin D by the irradiation.

Ultraviolet irradiation has been widely used in the treatment of certain diseases, but it has also

been recommended on less secure grounds both as a general "tonic" and as a means of preventing and correcting minor conditions of ill health. The increased use of artificial light in work places and the black-out conditions prevailing in many localities during the war years encouraged the prophylactic use of sources of artificial sunlight in factories, mines and offices. There is no convincing evidence, however, of the value of such uses for ultraviolet irradiation. It has been claimed that a few minutes' exposure to the rays of a quartz mercury-arc lamp each week is equivalent to some hours of natural sun bathing. From this has arisen the far more reaching claim that a course of such exposures reduces the amount of absenteeism due to accidents, common colds and general ill health.

It is now a simple matter to administer ultraviolet treatment to large numbers of workers with a relatively small loss of working time, and it would be quite easy to apply such therapy to large proportions of the employees in industrial and other occupations were it actually proved to have the good general effects attributed to it. In view of the conflicting nature of the previous evidence on the subject, the Industrial Health Research Board of the Medical Research Council of Great Britain considered it highly desirable to sponsor a well controlled and relatively large-scale inquiry into this important subject. The study was carried out by Dr Dora Colebrook, and her excellent report was recently published*.

The effects of ultraviolet irradiation on the health of clerical and industrial workers in three separate communities were investigated in Great Britain during the winter of 1944-1945. The criteria used were as follows: the amount of absenteeism due to sickness in all the groups, the duration of colds among clerical and factory workers and the absenteeism due to injuries and other causes among miners. In each community the group of persons receiving the full range of rays from mercury-arc lamps was compared with two control groups—a treated group irradiated with lamps of the same type but from which the shorter ultraviolet rays were cut off and an untreated group. The treated

*Colebrook, D. *Artificial Sunlight Treatment in Industry. A report of results of three trials—in an office, a factory and a coal mine.* Industrial Health Research Board Report, No. 89. 64 pp. London: His Majesty's Stationery Office 1946.

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Middlesex University School of Medicine, 1938 Sponsor Peer P Johnson, 1 Monument Square, Beverly

Henry D Stebbins, *Secretary*
342 Essex Street, Salem

FRANKLIN DISTRICT

- FAILLA, JOHN A, 48 Haywood Street, Greenfield
Boston University School of Medicine, 1939

Harry L Craft, *Secretary*
Ashfield

HAMPDEN DISTRICT

- ANTON, HARRY J, 175 Main Street, Three Rivers
University of Vermont College of Medicine, 1940
- APPEL, JOHN F, 42 Brookline Avenue, Holyoke
Jefferson Medical College of Philadelphia, 1941
- CHENEY, ROGER H, 80 Bennington Street, Springfield
University of Pennsylvania School of Medicine, 1940

- D'AVANZO, CHARLES S, 445 Cold Spring Avenue, West Springfield
New York Medical College, Flower and Fifth Avenue Hospitals, 1935

- DIAMOND, CHARLES A, 71 Park Avenue, West Springfield
New York Medical College, Flower and Fifth Avenue Hospitals, 1943

- FLETCHER, KENNETH S, 15 Otis Street, Chicopee Falls
Boston University School of Medicine, 1943

- JOFFE, ELLIS, 235 Beech Street, Holyoke
Brussels University School of Medicine, 1933 Sponsor Patrick Gear, 188 Chestnut Street, Holyoke

- LEANI, ALDO, 22 Horace Street, Springfield
University of Vermont School of Medicine, 1934

- MANDEVILLE, ERNEST A, 255 Chestnut Street, Holyoke
Tufts College Medical School, 1919

- MORRIS, LLOYD E, 3 Wenonah Place, Longmeadow
Ohio State University College of Medicine, 1940

- MOSIG, WILLIAM, 90 Pilgrim Road, Springfield
New York University College of Medicine, 1936

- VISCONTI, JAMES J, 680 Westfield Street, West Springfield
Midwest Medical College, 1935 Sponsor Arthur H Riordan, 20 Maple Street, Springfield

George C Steele, *Secretary*
39 Upper Church Street, West Springfield

HAMPSHIRE DISTRICT

- TATLOCK, HUGH, 50 Dryads Green, Northampton
Harvard Medical School, 1938

- WHARTON, RUSSELL S, Veterans Administration Hospital, Northampton
University of Arkansas School of Medicine, 1929

Mary P Snook, *Secretary*
Worthington

MIDDLESEX EAST DISTRICT

- HORNELL, ROBERT S, 26 Poplar Street, Melrose
Harvard Medical School, 1939

Roy W Layton, *Secretary*
8 Porter Street, Melrose

MIDDLESEX NORTH DISTRICT

- BLECHMAN, BENJAMIN, 858 Chelmsford Street, Lowell
Leipzig University, 1936 Sponsor Harry R Coburn, 202 Merrimack Street, Lowell

- BOARDMAN, DONNELL W, Main Street, Acton
Columbia University College of Physicians and Surgeons, 1939

- CROCKER, OSCAR, Park Street, Pepperell
Middlesex University School of Medicine, 1932 Sponsor J Edmund Boucher, 32 Middlesex Street, North Chelmsford

- HEIFITZ, FRANK M, 54 Canton Street, Lowell
Tufts College Medical School, 1943

- L'HOMME, LOUIS P, 240 West 6th Street, Lowell
College of Physicians and Surgeons, Boston, 1919 Sponsor John J McNamara, 133 Clark Road, Lowell

- LIGHTMAN, MASHE U L, 602 Wilder Street, Lowell
Middlesex University School of Medicine, 1940 Sponsor Archibald R Gardner, 16 Shattuck Street, Lowell

- QUINN, EDWARD M, JR, 118 Wentworth Avenue, Lowell
Tufts College Medical School, 1944

- SABA, EDWARD, 23 Butterfield Street, Lowell
Tufts College Medical School, 1944

- WILLIS, ALBERT W, 5 Burgess Street, Lowell
Tufts College Medical School, 1943

Brendan D Leahey, *Secretary*
9 Central Street, Lowell

MIDDLESEX SOUTH DISTRICT

- ADLER, MORRIS H, 130 Washington Street, Newton
University of Vienna, 1936 Sponsor Samuel J Kowal, 483 Beacon Street, Boston

remained in civilian practice, it is obvious that practically all of them must be answered if a broad representation of facts, experiences and opinions is to be obtained. Every physician who receives the questionnaire should fill it out promptly and return it immediately, whether or not he signs his name is optional.

MASSACHUSETTS MEDICAL SOCIETY BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups, such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of dates can be avoided.

DEATHS

CALDICOTT—Francis S. Caldicott, M.D., of Lowell, died January 17. He was in his fifty-eighth year.

Dr. Caldicott received his degree from Tufts College Medical School in 1913.

His widow survives.

KINGSLEY—Frederick Kingsley, M.D., of Chestnut Hill, died February 1. He was in his sixty-seventh year.

Dr. Kingsley received his degree from Queens University Faculty of Medicine, Kingston, Ontario, in 1905. He was a fellow of the American Medical Association.

His widow, two sons and a daughter survive.

NOBLE—Mary E. G. Noble, M.D., of Brookline, died February 16. She was in her seventy-fifth year.

Dr. Noble received her degree from Tufts College Medical School in 1902. She was psychiatrist at the Boston State Hospital for thirty-eight years, and was a member of the New England Society of Psychiatry and the Massachusetts Psychiatric Society.

Two nieces and a nephew survive.

PATCH—William T. Patch, M.D., of Roxbury, died February 7. He was in his eighty-sixth year.

Dr. Patch received his degree from New York University Medical College in 1890. He was a fellow of the American Medical Association.

RICHARDSON—Mark W. Richardson, M.D., of Newton Center, died February 12. He was in his eightieth year.

Dr. Richardson received his degree from Harvard Medical School in 1894. For a number of years he was a member of the former State Board of Health, and until his retirement several years ago he had served as medical director of the Equitable Life Insurance Company. He was a member of the Association of American Physicians and a fellow of the American Medical Association.

A son and three daughters survive.

ROSE—Wilfred A. Rose, M.D., of Lawrence, died September 24. He was in his forty-second year.

Dr. Rose received his degree from Tufts College Medical School in 1930.

His widow, a son and a daughter survive.

APPLICANTS FOR FELLOWSHIP

PUBLISHED IN ACCORDANCE WITH THE PROVISIONS OF CHAPTER V, SECTION 2, OF THE BY-LAWS

BARNSTABLE DISTRICT

BOURNE, GEORGE C., 227 Winter Street, Hyannis
Tufts College Medical School, 1944

GOULD, JOEL C., County Road, Pocasset
Kansas City University of Physicians and Surgeons, 1941
Sponsor: Julius G. Kelley, Pocasset

HOLLAND, CHARLES L., 475 East Main Street, Falmouth.
St. Louis College of Physicians and Surgeons, 1923. Sponsor: Thomas A. Wiswall, Falmouth.

JONAS, NORMAN W., Barnstable County Sanatorium, Pocasset.
Chicago Medical School, 1941. Sponsor: Julius G. Kelley, Pocasset.

ORCHARD, NORRIS G., South Harwich
Johns Hopkins University School of Medicine, 1907

RICE, JACKSON, 394 South Street, Hyannis
Middlesex University School of Medicine, 1931. Sponsor: Arthur D'Eha, Harwichport.

SHARPLES, ARTHUR B., 496 South Street, Hyannis
University of Vermont College of Medicine, 1934

TAVARES, CHARLES M., JR., Main Street, East Falmouth
Middlesex University School of Medicine, 1933. Sponsor: Paul P. Henson, 149 Main Street, Hyannis.

WRIGHT, WALTER E., Bridge Road, Orleans
Cornell University Medical College, 1943

Oscar S. Simpson, Secretary
Main Street, Centerville

BERKSHIRE DISTRICT

ALBANO, PETER R., 32 Benton Avenue, Great Barrington
Middlesex University School of Medicine, 1936. Sponsor: Maurice S. Eisner, 100 North Street, Pittsfield.

HIRSCHMANN, KURT L., Pittsfield
University of Munich, 1932. Sponsor: Maurice S. Eisner, 100 North Street, Pittsfield.

JUDSON, HARRY E., 74 North Street, Pittsfield
Syracuse University College of Medicine, 1943

LENT, SYLVESTER M., Taylor Street, Hinsdale
Middlesex University School of Medicine, 1937. Sponsor: Harry H. Bard, 74 North Street, Pittsfield.

LORD, WILLIAM J., 32 Hollenbeck Avenue, Great Barrington
Albany Medical College, 1939

WILDMAN, CHAIM J., 38 Daniels Avenue, Pittsfield
University of Vienna, 1937. Sponsor: V. J. Breen, 74 North Street, Pittsfield.

WILSON, FRANKLIN L., Stockbridge
Middlesex University School of Medicine, 1936. Sponsor: George S. Reynolds, 100 North Street, Pittsfield.

Daniel N. Beers, Secretary
74 North Street, Pittsfield

BRISTOL NORTH DISTRICT

LAWRENCE, BRADFORD W., 26 Dean Street, Attleboro
Tufts College Medical School, 1943

William J. Morse, Secretary
34 Sanford Street, Attleboro

BRISTOL SOUTH DISTRICT

BRYAN, BURTON D., 162 French Street, Fall River
University of Vermont College of Medicine, 1940

BURGER, HAROLD, 1 Clinton Place, New Bedford
Boston University School of Medicine, 1930

CONNORS, RAYMOND J., 87 Shawmut Avenue, Fall River
Harvard Medical School, 1931

LYLE, WALTER I., 426 Main Street, Wareham
Middlesex University School of Medicine, 1932. Sponsor: Raymond D. Stillman, 243 Main Street, Wareham.

MANELIS, SAMUEL R., 25 Chancery Street, New Bedford
Boston University School of Medicine, 1940

HASENBUSH, LESTER L, 690 Blue Hill Avenue, Dorchester
Johns Hopkins University School of Medicine, 1938

HEPBURN, JAMES P, 36 Governor's Road, Milton
Tufts College Medical School, 1942

KAGAN, SAMUEL, 1405 Beacon Street, Brookline
Midwest Medical College, 1935 Sponsor Arthur Berk,
Brookline

KARPATI, OSCAR, 3 Brewster Terrace, Brookline
Royal Hungarian Elizabeth University, 1926 Sponsor
Isaac R. Jankelson

LEONARD, FIELD C, 16 Parkway Road, Brookline
Harvard Medical School, 1940

LYONS, MELVIN K, 86 Floyd Street, Dorchester
Boston University School of Medicine, 1943

MANN, HAROLD E, 591 Morton Street, Dorchester
University of Pennsylvania School of Medicine, 1944

MATZ, MYRON H, 30 Alpha Road, Dorchester
University of Minnesota Medical School, 1939

MERRICK, EDWARD M, 115 Blue Hills Parkway, Milton
Middlesex University School of Medicine, 1941 Sponsor
John A Seth, 1550 Blue Hill Avenue, Dorchester

MILLER, HAROLD I, 1067A Blue Hill Avenue, Dorchester
Boston University School of Medicine, 1941

O'DAY, JOHN J, 278 Railroad Avenue, Norwood
Tufts College Medical School, 1941

POWERS, WILLIAM J, JR., 308 Massapoag Avenue, Sharon
Tufts College Medical School, 1943

PRICE, WILLIAM B, 62 Clifford Street, Roxbury
Meharry Medical College, 1939

ROSSMAN, BENNY, 1382 Beacon Street, Brookline
University of Marburg, 1921 Sponsor Carl Dahlen, 1620
Beacon Street, Brookline

RUBEN, MAURICE R, 40 Hansborough Street, Dorchester
Boston University School of Medicine, 1939

STANLEY, EDITH D, 37 Garrison Road, Brookline
Temple University School of Medicine, 1940

STRAUSS, LOUIS, 483 Talbot Avenue, Dorchester
Middlesex University School of Medicine, 1940 Sponsor
Hyman Morrison, Brookline

SUNSHINE, SAMUEL, 487 Adams Street, Milton
Middlesex University School of Medicine, 1941 Sponsor
Norman Welch, 644 Weld Street, West Roxbury

WEISMAN, WILLIAM S, 48 Hazelton Street, Mattapan
Middlesex University School of Medicine, 1933 Sponsor
John W Spellman, Chestnut Hill

Basil E Barton, *Secretary*
10 Richmond Street, West Roxbury

NORFOLK SOUTH DISTRICT

BROUGHAM, MILTON F, 100 Haviland Street, Wollaston
Harvard Medical School, 1940

COTLAN, WILLIAM P, 111 South Franklin Street, Holbrook
Middlesex University School of Medicine, 1933 Sponsor
Frank W Crawford, 98 North Franklin Street, Holbrook

EICHWALD, ERNST J, 77 Colonial Road, North Weymouth
Albert-Ludwig University, Freiburg, Germany Sponsor
James T Cameron, 1400 Hancock Street, Quincy

GARLAND, DONALD M, 105 Bickford Road, East Braintree
Tufts College Medical School, 1942

KNAPP, ALLEN H, 115 Monroe Road, Quincy
Yale University School of Medicine, 1935

KRASNER, GEORGE D, 26 Francis Avenue, Quincy
Faculty of Medicine University of Basel, Switzerland, 1937
Sponsor William S Altman, 32 Spear Street, Quincy

McIVER, JOHN M, 27 Governor Long Road, Hingham
Boston University School of Medicine, 1939

SHEA, DANIEL F, 51 Verchild Street, Quincy
Georgetown University School of Medicine, 1941

SULLIVAN, ARTHUR P, 11 Grove Street, Quincy
Tufts College Medical School, 1943

THOMPSON, RUSSELL F, 359 North Main Street, Randolph
Middlesex University School of Medicine, 1939 Sponsor
Harold R Record, 408 Commercial Street, East Braintree
Ebenezer K Jenkins, *Secretary*
Norfolk County Hospital, South Braintree

PLYMOUTH DISTRICT

DEACON, WALTER E, 1 Depot Street, South Duxbury
Tufts College Medical School, 1941

GOODSTONE, SAMUEL B, 10 Brewster Street, Plymouth
Harvard Medical School, 1924

SARKISIAN, SARKIS A, 616 Main Street, Bridgewater
Boston University School of Medicine, 1943

WILDER, FRANCIS D, 275 Boylston Street, Brockton
University of Lausanne, 1938 Sponsor Ralph C McLeod,
Goddard Hospital, Brockton
Ralph C McLeod, *Secretary*
Goddard Hospital, Brockton

SUFFOLK DISTRICT

ALEXANDER, FRED, Massachusetts General Hospital, Boston
University of Maryland School of Medicine, 1941

CAHAN, ALVIN M, 214 Riverway, Boston
Cornell University Medical College, 1940

FELDMAN, JOSEPH D, 41 Park Drive, Boston
Long Island College of Medicine, 1941

GEISS, GEORGE W, 42 Grove Street, Boston
Middlesex University School of Medicine, 1933 Sponsor
Winthrop Wetherbee, Jr, 24 School Street, Boston

LATORELLA, JOHN D, 117 Bartlett Road, Winthrop
Middlesex University School of Medicine, 1937 Sponsor
Pasquale Costanza, 238 Maverick Street, East Boston

LIVINGSTONE, ROBERT G, 572 Huntington Avenue, Boston
Harvard Medical School, 1942

MIDDLEBROOK, GARDNER, 400 West 119th Street, New York
City
Harvard Medical School, 1944

MILLER, JULIUS Y, 1318 Commonwealth Avenue, Allston
Tufts College Medical School, 1938

MURPHY, ROSEMARY A, 239 Commonwealth Avenue, Boston
Boston University School of Medicine, 1942

O'BRIEN, PAUL A, 156 Somerset Avenue, Winthrop
Tufts College Medical School, 1943

PANDOLFINO, JOSEPH E, 18 Winchester Street, Boston
Tufts College Medical School, 1943

RUZICKA, EDWIN R, 62 Crosby Road, Chestnut Hill
University of Maryland School of Medicine, 1939

SANBORN, EARL B, 711 West 171st Street, New York City
Northwestern University Medical School, 1942

SCIACCA, GUY F, 23 Unity Court, Boston
Middlesex University School of Medicine, 1939 Sponsor
Gerardo M Balboni, 78 Mt Vernon Street, Boston

SIEGEL, ROBERT, 489 Beach Street, Revere
Laval University Faculty of Medicine, 1942

STEVENSON, STUART S, 233 Beacon Street, Boston
Yale University School of Medicine, 1939

TUCKER, WALTER I, 629 Commonwealth Avenue, Boston
Harvard Medical School, 1939

WEINBERGER, JEROME L, 117 Bay State Road, Boston
New York University College of Medicine, 1938

WOLL, EPHRAIM, 107 Avenue Louis Pasteur, Boston
Creighton University School of Medicine, 1942

ZAMBELLA, JOSEPH, 36 Villa Avenue, Winthrop
Kansas City University of Physicians and Surgeons, 1937
Sponsor G Lyman Gately, 624 Bennington Street, East
Boston

Robert L Goodale, *Secretary*
330 Dartmouth Street, Boston

- ARTHURS, ALEXANDER T, 382 Broadway, Somerville
Middlesex University School of Medicine, 1936 Sponsor
Edgar F Sewall, 380 Broadway, Somerville
- BARONE, HENRY, 549 Washington Street, Newton
Middlesex University School of Medicine, 1930 Sponsor
Joseph Barone, 342 Commonwealth Avenue, Boston
- BARTON, DAVID J, 107 Ferry Street, Everett
Johns Hopkins University School of Medicine, 1941
- BEAKEY, JOHN F, 11 Forest Street, Cambridge
Tufts College Medical School, 1943
- BEER, FRED A, 234 Main Street, Waltham
Friedrich-Wilhelm University, Germany, 1931 Sponsor
Joseph Factor, 475 Commonwealth Avenue, Boston
- BLUTE, JAMES F, JR, 12 Walnut Street, Watertown
Harvard Medical School, 1942
- BRIDGES, WILLIAM C, 1016 Beacon Street, Newton Centre
Yale University School of Medicine, 1940
- BURNETT, CHARLES H, 40 Clyde Street, Newtonville
University of Colorado School of Medicine, 1937
- BYRNE, JOHN J, 125 Newton Street, Weston
Harvard Medical School, 1941
- CARDILLO, EDWARD M, 534 Broadway, Everett
Middlesex University School of Medicine, 1940 Sponsor
Frank Mirabello, 324 Broadway, Everett
- CHALMERS, THOMAS C, JR, 17 Lowell Street, Cambridge
Columbia University College of Physicians and Surgeons,
1943
- CLANCY, GEORGE F, 15 Warren Avenue, Marlboro
Georgetown University School of Medicine, 1942
- CLEARY, ROBERT V, 410 Memorial Drive, Cambridge
Harvard Medical School, 1939
- DANA, JACOB B, 1957 Commonwealth Avenue, Brighton
Boston University School of Medicine, 1943
- FLEMING, WILLIAM L, 76 Walden Street, Newtonville
Vanderbilt University School of Medicine, 1932
- FOSTER, GEORGE B, JR, Hotel Commander, Cambridge
Jefferson Medical College, 1907
- GELLIS, SYDNEY S, 71 Grozier Road, Cambridge
Harvard Medical School, 1938
- GRAHAM, JOHN B, 107 Greenlawn Avenue, Newton Centre
Harvard Medical School, 1940
- HARRIS, CASIMIR P, 21 Duffield Road, Auburndale
Tufts College Medical School, 1941
- HUNTER, JOHN J, 61 Langdon Street, Cambridge
Tufts College Medical School, 1943
- LEAVELL, HUGH R, 125 Coolidge Hill, Cambridge
Harvard Medical School 1926
- LEAVITT, JOSEPH S, 318 Clifton Street, Malden
University of Lausanne Faculty of Medicine, 1936 Sponsor
Harry L McDonald, 414 Pleasant Street, Malden
- MAGWOOD, ROBERT W, 27 Stone Avenue, Somerville
Tufts College Medical School, 1943
- MATLOFF, JACOB, 17 Kirkwood Road, Brighton
Boston University School of Medicine, 1943
- MEROLA, JOSEPH F, 197 High Street, Waltham
Middlesex University School of Medicine, 1935 Sponsor
Ralph Mankowich, 29 Barbara Road, Waltham
- MORRISON, JOHN L, 45 Milner Street, Waltham
University of Pennsylvania School of Medicine, 1938
- MUCCI, ALFRED C, 420 Broadway, Somerville
Middlesex University School of Medicine, 1935 Sponsor
Frank F Scigliano, 99 Highland Avenue, Somerville
- PAGEL, MAX M, 21 Clark Street, Newton Centre
University of Breslau, 1920 Sponsor Bentley P Colcock,
78 Hull Street, Newtonville
- ROBINSON, HENRY S, 9 Aldersey Street, Somerville
Kansas City University of Physicians and Surgeons, 1939
Sponsor Philip P McGovern, 1525 Cambridge Street,
Cambridge
- SHANE, THEODORE, 80 Waltham Street, West Newton
Middlesex University School of Medicine, 1939 Sponsor
David Ayman, 520 Beacon Street, Boston
- SIMONEAU, ARTHUR G, 18 Grant Street, Marlboro
Boston University School of Medicine, 1939
- STANTON, JOSEPH R, 114 Shorncliffe Road, Newton
Yale University School of Medicine, 1945
- STONE, CHAUNCEY M, JR, 143 Oakland Avenue, Arlington
Boston University School of Medicine, 1943
- SWEETSER, ELLIOTT H, 24 Florence Street, Malden
Boston University School of Medicine, 1943
- THOMPSON, CHARLES A, 1145 Walnut Street, Newton High
lands
Tufts College Medical School, 1943
- WHITNEY, KARL R, Pokonoket Road, South Sudbury
Tufts College Medical School, 1939
- WORTHINGTON, RICHARD V, Cushing Veterans Admini-
stration Hospital, Framingham
Yale University School of Medicine, 1938
- ZOVICKIAN, ANTHONY, 528 Mt Auburn Street, Watertown.
Yale University School of Medicine, 1943
- Alexander A Levi, Secretary
481 Beacon Street, Boston

NORFOLK DISTRICT

- BICCHIERI, N ANTHONY, 474 Canterbury Street, Roslindale.
St George's Hospital Medical School, University of London,
1935 Sponsor Theodore F Lindberg, Boston State Hos-
pital, Dorchester
- BINDER, ABRAHAM I, 185 Winchester Street, Brookline
Boston University School of Medicine, 1940
- BRESNICK, ELLIOTT, 91 Beals Street, Brookline
Tufts College Medical School, 1943
- BREWSTER, HENRY H, 760 Brush Hill Road, Milton
Harvard Medical School, 1938
- BROWN, ROBERT H, 5 Garfield Street, Foxboro
Harvard Medical School, 1943
- CAMPBELL, ELMORE M, 33 Howe Street, Dorchester
Tufts College Medical School, 1944
- CAMPBELL, JAMES B, 140 Moss Hill Road, Jamaica Plain
Harvard Medical School, 1935
- CHASEN, MIGNON C, Boston State Hospital, Dorchester
Royal University of Palermo, Italy, 1935 Sponsor Walter
E Barton, Boston State Hospital, Dorchester
- CHASEN, WILLIAM H, 474 Canterbury Street, Roslindale
University of Lausanne, 1937 Sponsor John S Thornton,
1890 Beacon Street, Brookline
- CREHAN, JOSEPH P, 16 Avalon Road, West Roxbury
Boston University School of Medicine, 1943
- DAIELL, SAUL S, 19 Mount Vernon Street, West Roxbury
Louisiana State University School of Medicine, 1941
- DAVIS, JEAN P, 28 Avon Road, Wellesley
Yale University School of Medicine, 1943
- ELWYN, SIDNEY L, 783 Washington Street, Dorchester
Middlesex University School of Medicine, 1941 Sponsor
George A Small, 81 Walpole Street, Norwood
- FISHER, H BERNARD, 14 York Street, Dorchester
Tufts College Medical School, 1938
- FITZGERALD, JAMES A, 82 Perry Street, Brookline
Harvard Medical School, 1943
- GARRIGUES, HENRY B, 47 Webster Street, Needham
Harvard Medical School, 1937
- GILBERT, JOHN J, 241 Humboldt Avenue, Roxbury
Middlesex University School of Medicine, 1936 Sponsor
Rubin Guralnick, 87 Maple Street, Roxbury
- GLICKMAN, ABRAHAM J, 11 Wilcock Street, Dorchester
University of St Vladimir Faculty of Medicine, Kiev,
1904 Sponsor Myer Herman, 1071 Blue Hill Avenue,
Dorchester
- GOLUB, LEON M, 90 Corbet Street, Dorchester
Boston University School of Medicine, 1945
- GORE, MAX, 107 Blue Hill Avenue, Roxbury
Midwest Medical College, 1937 Sponsor Jacob Apple-
baum, 371 Commonwealth Avenue, Boston
- GUCCIONE, I JOSEPH, 91 Belgrade Avenue, Roslindale
Middlesex University School of Medicine, 1939 Sponsor
Timothy P Lyons, Milton
- GUCKER, THOMAS, 100 High Street, Brookline
University of Pennsylvania School of Medicine, 1941

17 Diseases, Nutrition and Metabolism By Erich Urbach, D. With the collaboration of Edward B. LeWinn, M.D., cloth, 634 pp., with 266 illustrations and 112 tables. New York: Grune and Stratton, 1946. \$10.00.

English-speaking dermatologists owe the author a debt of gratitude for this stupendous encyclopedia of thirteen hundred references on the various aspects of nutrition and cutaneous metabolism. The book is divided into four parts. Part I deals with the influence of nutrition on the physiology of the skin. Part II describes the nutritional causes of dermatoses. The influence of diseases of the gastrointestinal tract, liver and pancreas on the skin is the subject matter of Part III. In Part IV the nutritional therapy of skin diseases is reviewed. There are over one hundred tables, in which are included many useful diets. The two hundred and sixty-six illustrations are excellent.

The compilation of the information so essential to the investigator and dermatologist required limitless patience and energy. This, however, is a fact familiar to those who have known the author for the past twenty years and who have read his writings in numerous journals. The volume should be a stimulus for further research in this somewhat neglected field of cutaneous medicine. The average dermatologist has little faith in the value of dietary therapy. Perhaps this is due to his lack of knowledge, or to disappointment in his results after following the enthusiastic recommendations of Dr. Urbach and other workers in this field.

All dermatologists and students of nutrition should have this book in their library, for they can use it with discrimination. Because of its many theoretical contraindications, however, the reviewer hesitates to recommend it to the student and general practitioner, unless he has had excellent basic training in biochemistry.

1 History of Medicine By Douglas Guthrie, M.D., F.R.C.S. (Edin.), F.R.S.E. With an introduction by Samuel C. Harvey, M.D. 8°, cloth, 448 pp., with 72 plates. Philadelphia: J. B. Lippincott Company, 1946. \$6.00.

This book appeared in England and on this side of the Atlantic at about the same time. In England it was put out by Thomas Nelson and Sons, whereas in the United States its publisher bears a different name. Yet, so far as can be ascertained, the two imprints are identical in pagination, illustrations and content.

The *British Medical Journal*, the *Bulletin of the History of Medicine*, the *Journal of the Association of American Medical Colleges* and the *Lancet* have reviewed this work. All but the *Bulletin of the History of Medicine* gave high praise to what the author had attempted and his manner of work, the review in the *Bulletin* is more critical and seems a trifle capricious.

As a matter of fact, this lively history of medicine from its earliest days to the present is readable, informative and entertaining. Although a professional historian can easily pick flaws in a work of this character, the ordinary reader will have little cause for complaint. The material is presented in an orderly way and is well indexed, the typography is good, the illustrations are apt, the literary style is admirable, and at the end of each chapter is listed a selection of material for further reading on the topic under discussion, so that earnest amateurs are well guided.

The book was placed on the shelf in one of the medical-school libraries along with several other books of current interest. The reaction of the students was unusual: a great many looked through the volume and glanced at the pictures, several sat down to read the book seriously, so that it was difficult to keep it in place, and a few wished to know how to obtain copies for themselves, saying that it seemed exactly the type of medical-history text for which they had been seeking. Such an opinion from students is about as complimentary as possible. On the whole, a taste for medical history develops late, and thus any well written book on the subject that attracts medical students commands respect. It may prove to be the cornerstone to many young people for years of pleasure.

The Ocular System. A handbook of roentgen diagnosis By Vincent W. Archer, M.D. 8°, cloth, 320 pp., with 148 plates. Chicago: The Year Book Publishers, Incorporated, 1945. \$5.50.

This handbook of roentgenologic diagnosis is a mine of useful information. It describes and shows in excellent illus-

trations the usual lesions found in the bones of both children and adults. The author states in his preface that the book is written for the occasional roentgenographer. In this, he achieves his purpose admirably. The book is well arranged, one does not need to search the index. The descriptions are concise and clear, and the reproductions of the x-ray films are almost without fault. Here is a good book both for the student and the experienced roentgenologist. It can be heartily recommended as the best handbook in its field.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Synopsis of Gynecology. Based on the textbook, *Diseases of Women*, by Harry S. Crossen, M.D., consulting gynecologist, Barnes, St. Louis Maternity and St. Luke's hospitals, and Robert H. Crossen, M.D., assistant professor of clinical gynecology and obstetrics, Washington University School of Medicine, assistant gynecologist and obstetrician, Barnes and St. Louis Maternity hospitals, and gynecologist, St. Luke's and DePaul hospitals. Third edition. 12°, cloth, 253 pp., with 132 illustrations. St. Louis: C. V. Mosby Company, 1946. \$3.00.

This third edition of a standard manual has been revised to date, and a new short chapter on medicolegal problems has been added, as well as many new illustrations.

The 1945 Year Book of Industrial and Orthopedic Surgery. Edited by Charles F. Painter, M.D., orthopedic surgeon, Massachusetts Women's and Beth Israel hospitals, Boston. 12°, cloth, 432 pp. Chicago: The Year Book Publishers, 1946. \$3.00.

This latest edition of a standard yearbook has expanded to some extent the amount of space allotted to industrial medicine and surgery. This volume should prove of value to all persons interested in orthopedic surgery and industrial medicine.

Transactions of the American Gynecological Society. Vol. 68, for the year 1944. Edited by Howard C. Taylor, Jr., M.D. 8°, cloth, 324 pp. St. Louis: C. V. Mosby Company, 1945.

This volume contains the various papers read at the annual meeting of the American Gynecological Society, held in June, 1944, in Hersey, Pennsylvania.

Virus as Organism. Evolutionary and ecological aspects of some human virus diseases. By Frank M. Burnet, M.D., F.R.S., director, Walter and Eliza Hall Institute of Research in Pathology and Medicine, Melbourne, Australia. Harvard University Monograph in Medicine and Public Health, No. 8. 8°, cloth, 134 pp. Cambridge: Harvard University Press, 1945. \$2.00.

This monograph is an expansion of the Dunham Lectures given at Harvard University in 1944. The author discusses some of the more important diseases of man from a consistently biologic point of view. Dr. Burnet's basic interpretation of virus disease is that viruses of micro-organisms have evolved by parasitic degeneration from larger micro-organisms, many of them in all probability from bacteria. The viruses survive by biologic reproduction, and the virus species, like any other living species, has found a way of indefinite survival. Dr. Burnet concludes that there is no escape from the pragmatic necessity of regarding viruses as living organisms reproducing their kind and subject to the same imperative of continued survival in a changing environment as other organisms. The first chapters consider the reproduction, variation and survival, evolution and change in virus disease, and the reaction of the host to virus infection. Following this there is a discussion of herpes simplex, poliomyelitis, psittacosis, smallpox, alastrim, vaccinia, yellow fever and influenza. A selected bibliography is appended to the text. This monograph, as well as all the other Harvard medical monographs, should be in all medical and public-health selections.

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MASSACHUSETTS DEPARTMENT
OF PUBLIC HEALTHBLOOD GROUPING AND Rh TYPING
OF PRENATAL BLOODS

For the present, the Massachusetts Department of Public Health has facilities for blood grouping and Rh testing of a limited number of prenatal bloods submitted by physicians

Each specimen must be accompanied by the form entitled "Request for Prenatal Blood Grouping and Rh Typing" that is properly filled in. These forms, which include directions, may be secured from the Wassermann Laboratory, 240 Longwood Avenue, Boston 17. The specimen is submitted in the department's regular Wassermann outfit, and the blood-grouping, the Rh-typing and the prenatal Hinton test can be conveniently performed on the same specimen

CONSULTATION CLINICS FOR CRIPPLED
CHILDREN IN MASSACHUSETTS UNDER
THE PROVISIONS OF THE SOCIAL
SECURITY ACT

CLINIC	DATE	CLINIC CONSULTANT
Salem	March 3	Paul W. Hugenberger
Haverhill	March 5	William T. Green
Lowell	March 7	Albert H. Brewster
Brockton	March 13	George W. Van Gorder
Springfield	March 18	Garry deN. Hough, Jr.
Pittsfield	March 19	Frank A. Slowick
Fall River	March 24	David S. Grice
Hyannis	March 27	Paul L. Norton

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments

BOOK REVIEWS

Public Health the American Way By H. B. Anderson 8°, cloth, 238 pp. New York: Citizens Medical Reference Bureau, Incorporated, 1945. \$2.50

This volume is a compilation of short abstracts interspersed with statements by the author, who is secretary-treasurer of the Citizens Medical Reference Bureau, Incorporated. The purpose of this bureau is stated in its certificate of incorporation: "To preserve, establish, maintain and safeguard through publicity and other lawful means, the right of adults or, in the case of minors, the right of parents or guardians to determine the form or manner of treatment or care to be prescribed or applied for the cure or prevention of disease."

Although some of the quotations in the book are of recent origin and from prominent physicians, others are not. The following are excerpts:

for all practical purposes smallpox of a virulent character in the United States is an imaginary disease the presence or absence of classical or virulent smallpox bears no relation whatever to the vaccination laws of any country but it does bear a direct relationship to the progress of the respective countries in the improvement of sanitary and general living conditions. Many persons have learned how to live so that to them it is natural to be healthy without the aid of medical products of any kind and they want to be left alone so they can continue to be naturally healthy.

It is doubtful whether this book will be of interest to many members of the medical profession.

The Principles and Practice of Tropical Medicine By L. Everard Napier 8°, cloth, 917 pp., with 195 illustrations and 32 tables. New York: The Macmillan Company, 1946. \$11.00

Napier's approach to tropical medicine is distinctive. The style is readable and suggests at times the informal clinical lecture. In general, the material is presented systematically, simply and clearly.

The chapters dealing with the diseases of India, which the author knows well, are excellent. This is notably true of the chapter on kala-azar. The importance of malaria has been emphasized, as it should be, by the devotion of many pages to this subject.

Unfortunately, some of the helminthic diseases have been less well handled, and some old errors have been perpetuated. For example, the map showing the distribution of bancroftian filariasis indicates that the disease exists in parts of the Belgian Congo in which *Wuchereria bancrofti* is not indigenous. The names *Trichuris trichiura* and *Trichocephalus trichiura* are used interchangeably to designate the former. Iceland is listed first among the important foci of hydatid disease, whereas the disease is practically nonexistent there today. Its occurrence in England is not mentioned. The sections concerned with various kinds of tapeworms are separated from each other by chapters that deal with quite different kinds of helminthic diseases.

The chapter on climate and disease is interesting. The author's views on house construction and on air conditioning in the tropics are informative.

Some of the more important methods of laboratory diagnosis of tropical diseases are well described.

Many of the illustrations and diagrams are good, but a few might advantageously be improved or even omitted.

The New England Journal of Medicine

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Volume 236

MARCH 13, 1947

Number 11

ARTHRITIS IN THE MEDITERRANEAN THEATER OF OPERATIONS*

I Incidence of Joint Disease — Clinical Description of Rheumatoid Arthritis

LIEUTENANT COLONEL CHARLES L. SHORT, M.C., A.U.S.

LIKE other organs of the body, the joints are subject to many different forms of disease and injury of both known and unknown etiology. Since this paper deals chiefly with the medical aspects of joint disorders, strictly surgical conditions, such as the immediate effects of trauma and articular infection associated with wounds, have been excluded. Diseases and injuries of the bones, muscles, tendons, bursas and other supporting structures were not studied unless there was subjective or objective evidence pointing toward joint involvement. The conditions variously labeled arthralgia, myositis, myalgia and fibrositis, although not strictly forms of arthritis, were included, since they are often confused with actual joint disease clinically and are usually put under the heading of arthritis in military medical statistics; furthermore, these diagnoses were frequently encountered in the case records in the Theater and bore a high rate of disability. Again, what may be called psychogenic or psychosomatic rheumatism formed an object of study. Although belonging to the neuroses, this condition bears a relation to the handling of joint disease that is even more important under military conditions than in civilian life. Low-back pain was excluded from consideration, unless actually due to arthritis or forming a part of the symptomatology of the arthralgia or psychogenic rheumatism group. Finally, rheumatic fever, although having certain features in common with rheumatoid arthritis and occasionally mistaken for one of the arthritides, was regarded as an independent, generalized disease and was therefore considered only in the differential diagnosis.

Material for this study was gathered from epidemiologic data available at the offices of the Surgeon, Fifth Army, and of the Theater Surgeon, from hospital records, by questionnaires sent to general hospitals, by conferences with medical officers throughout the Theater and by personal observations.

INCIDENCE OF ARTHRITIS

No over-all figures were available to determine the incidence of the arthritic diseases† among American troops in the Theater. Samples, chiefly from hospital admissions, dispositions or patients remaining, however, were utilized to give a rough indication of the extent of the problem. The six evacuation hospitals serving the Fifth Army in August, 1944, are considered first. During one week 2149 soldiers were admitted to these hospitals for disease. Those complaining of nontraumatic musculoskeletal disorders numbered 128, or 3.4 per cent, of the total. The dispositions to duty or to the base for the month of August, 1944, are shown in Table 1. Although the arthritic diseases made up only a small proportion of either the weekly (3.4 per cent) or the monthly (3.1 per cent) dispositions, it is possible that the incidence would have been increased in figures obtained during months of rain and cold.

Table 2 presents the breakdown of medical admissions to a station hospital from August, 1943, through April, 1945. Again, conditions grouped under the heading "arthritis" made up a small proportion of the total—6.5 per cent of the non-infectious cases and 1.8 per cent of the total admissions to the medical service. When the arthritic patients admitted to general hospitals were enumerated, the rate was somewhat higher—1.8 per cent of total admissions and 4.1 per cent of patients entering the medical services (Table 3). Comparable figures were obtained from a study of the cases remaining in hospitals in the Peninsular Base Section on a given day of each month from March through November, 1944. The arthritic cases, including arthritis, myositis and myalgia, in the musculoskeletal group were separated from the remainder, consisting chiefly of low-back pain, pes planus and bone disease (Table 4). A daily average of 343 patients with arthritic diseases were hospitalized in this base section, making up 3.3 per

*The following material represents a condensation and a certain amount of revision of parts of a clinical monograph on arthritis prepared at the direction of the Surgeon, Mediterranean Theater of Operations, United States Army, and submitted to him in final form in June 1945.

†In this section the term "arthritic diseases" includes in both text and tables conditions diagnosed as arthralgia, myalgia, myositis and fibrositis.

A Future for Preventive Medicine By Edward J. Stuehlitz, MS, MD 8°, cloth, 77 pp. Studies of the New York Academy of Medicine Committee on Medicine and the Changing Order. New York: The Commonwealth Fund, 1945. \$1.00.

Dr. Stuehlitz presents the argument that the full achievement of preventive medicine requires the co-operation of the physician, the individual patient and the collective public. He points out that there are still many unexplored fields and urges more research in public health and medicine, particularly with reference to the health problems of middle and old age, better medical education and better public instruction. He believes that the conception of preventive medicine should be broad in scope. He divides his text into three parts: definitions pertaining to preventive medicine, including a classification of preventive activities, health over the last forty years, comprising a statistical study of morbidity and discussion of major present health hazards, and a program for preventive medicine, including its relation to environment, research and education and to the individual. A selected bibliography is appended to the text. This monograph should prove of value to all interested in public health and should be in all medical libraries.

NOTICES

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston
Lecture Hall, 9-10 a.m.

MEDICAL CONFERENCE PROGRAM

- Friday, March 7 — Cancer of the Stomach, 1937-1947. Dr. Robert M. Kark.
Wednesday, March 12 — Clinicopathological Conference. Drs. Robert P. McCombs and H. E. MacMahon.
Friday, March 14 — Carcinoma of the Cecum. Dr. Donald T. Chamberlin.
Wednesday, March 19 — Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon.
Friday, March 21 — Radioactive Iodine in Hyperthyroidism. Dr. Earle M. Chapman.
Wednesday, March 26 — The History of the Concept of Functional Nervous Disease. Dr. A. Warren Stearns.
Friday, March 28 — The Effect of Carotid Sinus Stimulation on Anginal Pain, and Other Considerations. Dr. Samuel Levine.

On Tuesday and Thursday mornings, Dr. S. J. Thannhauser will give medical clinics on hospital cases. On Saturday mornings, clinics will be given by Dr. William Dameshek. Medical rounds are conducted each weekday by members of the staff from 12:00 m. to 1:00 p.m. in the Lecture Hall.

All exercises are open to the medical profession.

TUFTS MEDICAL ALUMNI ASSOCIATION

The annual dinner meeting of the Tufts Medical Alumni Association will be held at 6:30 p.m. on Wednesday, March 26, at the Copley-Plaza Hotel, Boston. The guest speaker will be Thomas A. Hendricks, secretary of the Council on Medical Service of the American Medical Association, who will speak on the topic "Public Relations, Economics and the Doctor." President Leonard Carmichael of Tufts College will give a progress report. Dr. A. K. Paine, president of the Alumni Association, will speak on alumni affairs. Dr. John T. Batal, representing the twenty-five-year class, will speak on the subject "Time Marches On." Dr. Lewis B. Hayden, of Livermore Falls, Maine, will represent the fifty-year class. Dr. Dwight O'Hara will speak as dean of the Medical School and as president of the Massachusetts Medical Society. More than six hundred medical alumni are expected to attend this event. Dr. John J. Todd will preside.

AMERICAN COLLEGE OF SURGEONS

The fourth of a series of seven sectional meetings of the American College of Surgeons will be held in Providence on March 28 and 29, with headquarters at the Providence-Biltmore Hotel, Rhode Island and the surrounding states will participate. The medical profession at large, medical students and hospital personnel are invited to join with the fellows of the College in the meeting, which will be addressed by nationally prominent visiting and local speakers.

POSTGRADUATE INSTITUTE

The Eleventh Annual Postgraduate Institute of the Philadelphia County Medical Society will be held on the Rod Garden of the Bellevue-Stratford Hotel in Philadelphia on April 15, 16, 17 and 18. The theme of the meeting will be symposiums on medical progress. Among the subjects to be covered are thyroid disease, diabetes, vitamins and hormones, intestinal disorders, kidney pathology, peripheral vascular diseases, antibiotics, hypertension, diseases of the lung, neuropsychiatry, diseases of the stomach and duodenum, allergy, skin disorders and otolaryngologic diseases. There will also be two evening meetings at the building of the Philadelphia County Medical Society on the subjects of the disorders of childhood and infancy and of obstetric and gynecologic problems. There will be a complete array of technical exhibits, as well as a number of interesting scientific exhibits.

The registration fee for the entire course is \$5.00 for non-members of the society. Out-of-town physicians planning to attend the meeting are urged to make their hotel reservations immediately. Further information may be obtained from Gilson C. Engel, M.D., Director, 301 South 21st Street, Philadelphia 3.

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The March 25 lecture of the Tuesday evening lecture series of the House Officers' Association of the Boston City Hospital will be held in the new Cheever Amphitheater, Dowling Building, at 7:00. Dr. Cornelius P. Rhoads, director of the Memorial Hospital, New York City, will speak on the subject "The Metabolic Aspects of Cancer."

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MARCH 13

FRIDAY, MARCH 14

- *9:00-10:00 a.m. Carcinoma of the Cecum. Dr. Donald T. Chamberlin. Joseph H. Pratt Diagnostic Hospital.
*10:00 a.m.-12:00 p.m. Medical Staff Rounds. Peter Bent Brigham Hospital.
12:00 m.-1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

MONDAY, MARCH 17

- *12:15-1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, MARCH 18

- 12:00 m.-1:00 p.m. Dermatological Service, Grand Rounds. Amphitheater, Dowling Building. Boston City Hospital.
*12:15-1:15 p.m. Clinicoradiogenetological Conference. Peter Bent Brigham Hospital.

WEDNESDAY, MARCH 19

- *9:00-10:00 a.m. Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon. Joseph H. Pratt Diagnostic Hospital.
*11:00 a.m.-12:00 p.m. Medical Clinic. Amphitheater, Children's Hospital.
*12:00 m. Clinicopathological Conference (Children's Hospital). Amphitheater, Peter Bent Brigham Hospital.
*2:00-3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

*Open to the medical profession.

(Notices continued on page xvii)

hospital Officers from this hospital made up the Disposition Board for the Fifth Army. A total of 3991 patients with various conditions were reclassified for limited service between February 22, 1944, and May 1, 1945 (Table 7). The importance of arthritis is evident from these data, since these

TABLE 5 *Man-Days Lost through Hospitalization in the Mediterranean Theater*

PERIOD	MAN-DAYS LOST			AVERAGE NO OF ARTHRITIC PATIENTS IN HOSPITAL
	TOTAL	FOR ARTHRITIS	FOR DISEASE	
1943	4 016 000	59 000	2 704 000	244
1944	6 560 000	145 000	4 357 000	358
JANUARY to April 1945	1 871 000	41 000	1 247 000	341
TOTAL	12 457 000	275 000 (2%)	8 338 000 (67%)	

patients constituted the largest group among those reclassified for disease and were surpassed in the whole number only by neuropsychiatric cases and battle casualties.

During World War I, a total of 65,192 patients suffering from joint disease (exclusive of rheumatic fever) were admitted to Army hospitals.¹ Until the data for World War II are finally compiled, no comparison is possible, but owing to the greater size of the Army alone, it is probable that the total figure will be at least doubled. In 1941 about 35,000 veterans disabled by arthritis were receiving compensation, including, of course, those whose illness had started after discharge from the service. As yet, little has appeared in the literature on the military incidence of joint disease in World War II. The admissions to two British general hospitals in France in 1940 (during a period of combat inactivity) indicated a much higher incidence of arthritic disease in the British Army at that time than in the United States Army in the Mediterranean Theater.² In fact, 10 per cent of all those patients admitted to hospitals and 20 per cent of those entering the medical service referred their symptoms to the joints or other supporting structures (fibrositis). The experience of the Medical Division of a United States Naval Base Hospital operating at Casablanca

TABLE 6 *Disposition of Patients with Arthritis in General Hospitals Compared with That of Other Medical Patients*

SOURCE	TOTAL	DUTY		LIMITED SERVICE		EVACUATION	
		NO	PER CENTAGE	NO	PER CENTAGE	NO	PER CENTAGE
Arthritis							
Ten general hospitals (up to December 1, 1944)	2,938	956	32.6	602	23.4	1,280	44.0
45th General Hospital (Medical Service)	329	63	19.1	150	59.6	156	41.1
Diseases other than arthritis							
45th General Hospital (Medical Service)	5,222	3,341	64.1	554	10.2	1,347	25.7
Patients hospitalized for disease in Theater (January 1943 to April 1945)*	705,320	618,921	88.0	53,079	7.6	31,320	4.4

*Includes arthritic patients.

The number of patients evacuated from the Theater for arthritis may be estimated from a sample containing the distribution according to diagnoses of evacuees for disease from the Mediterranean Base Section from March 1 to June 1, 1944. (During this period most of the patients going to the Zone of the Interior from the Theater left via this base section.) If neuropsychiatric disorders were excluded, arthritis was outnumbered only by peptic ulcer and outranked such conditions as pulmonary tuberculosis, rheumatic fever with or without valvular heart disease, trench foot, asthma, malaria and nephritis (Table 8). The patients evacuated for disease from the Theater in 1943, 1944 and the first four months of 1945 numbered 31,320. Applying the ratio (5.0 per cent) found in Table 8 to this figure, the number evacuated for arthritis may be calculated at 1566. The true figure is somewhat higher, since the total until December 1, 1944, for this group of diseases from eleven of the fifteen general hospitals in the Theater amounted to 1507.

in 1943 and 1944 has recently been published.³ In the first year of operation, 36 cases (4.8 per cent) among 744 admissions were diagnosed as arthritis.

TABLE 7 *Distribution of Patients Classified for Limited Service by the Third Convalescent Hospital from February 22, 1944, to May 1, 1945*

TYPE OF CASE	NO OF CASES	PERCENTAGE OF TOTAL	PERCENTAGE OF DISEASE CASES
Neuropsychiatric	2,283	58.1	
Battle casualties (residual effects)	542	8.4	
Injuries	212	5.2	
Arthritis	284	7.0	24.8
Pes planus or pes cavus	237	5.7	20.8
Eye	133	3.2	11.5
Asthma or bronchitis	120	3.0	10.5
Ear	66	1.7	5.8
Trench foot	37	0.9	3.2
Miscellaneous	277	6.8	23.4
Total	3,991		

a proportion corresponding to that obtained in the three Army general hospitals cited in Table 3. Kinsey⁴ analyzed a series of 1000 patients separated

cent of the total of those with disease and 4.7 per cent of those with noncommunicable disease. On the basis of the percentage obtained in Table 4 an estimate was made of the man-days lost through hospitalization for arthritis in the Theater during 1943, 1944 and the first four months of 1945 (Table

TABLE 1 Dispositions to Duty or to the Base from Six Evacuation Hospitals Serving the Fifth Army in Italy during August, 1944

TYPE OF DISEASE	NO. OF CASES	PER- CENTAGE	RATE PER 1000 PER ANNUM
Gastrointestinal	1,147	15.3	88
Genitourinary	1,005	13.1	77
Skin	936	12.4	72
Respiratory	672	8.8	52
Neuropsychiatric	631	8.3	49
Eye, ear, nose and throat	530	7.3	40
Cardiovascular	333	4.5	25
Musculoskeletal, nontraumatic	235	3.1	18
Musculoskeletal, traumatic	171	2.2	13
Miscellaneous (malaria, sand fly fever and so forth)	1,912	25.0	150
Totals	7,572		584
Accidental injuries	1,235		97
Grand totals	8,807		681

5) The figure obtained was 275,000 man-days for this period of twenty-eight months.

The importance of arthritis as a cause of manpower loss was more significantly measured by the number of soldiers rendered unavailable for combat owing to reclassification for limited service or removed entirely from the Theater by evacuation than by the morbidity figures given alone. The liability of the arthritic patient to escape returning to full duty was suggested, however, by the slightly increased rate (4.1 per cent) found on the medical services of three general hospitals (Table 3), com-

TABLE 2 Classification of Patients Admitted to the Medical Service of the Seventy-Third Station Hospital (August, 1943, through April, 1945)

TYPE OF DISORDER	NO. OF CASES	PERCENTAGE OF TOTAL ADMISSIONS	PERCENTAGE OF NONINFECTIOUS CASES
Noninfectious			
Neuropsychiatric	669	4.9	18.3
Skin	607	4.5	16.6
Gastrointestinal	440	3.3	12.1
Arthritic	239	1.8	6.5
Miscellaneous	1,700	12.6	46.5
Totals	3,655	27.1	
Infectious	9,867	72.9	
Total	13,522		

pared with figures from other types of hospitals and for those in the Peninsular Base Section as a group. Any medical patient, of course, was less likely to return to full duty once in a general hospital but the data considered below demonstrate that a high percentage of those with joint disease failed to resume their previous duty status. Table 6 presents the combined figures for dispositions of patients with arthritis from ten general hospitals

as obtained from written questionnaires and from the records of the Medical Service of the Forty-Fifth General Hospital, with the period covered chosen

TABLE 3 Incidence of Arthritis in Admissions to Ten General Hospitals to December 1, 1944, and in Admissions to the Medical Service in Three

GENERAL HOSPITALS	TOTAL ADMISSIONS	CASES OF ARTHRITIS NO.	PERCENTAGE
Ten general hospitals	177,317	3,260	1.8
70th General Hospital (Medical Service)	5,916	274	4.6
45th General Hospital (Medical Service)	12,259	467	3.8
12th General Hospital (Medical Service)	10,076	416	4.2
Totals	28,251	1,157	
Average			4.1

to exclude the time when this hospital was receiving many patients from other general hospitals for evacuation. For comparison, the ratios of dispositions of the remainder of the medical patients in this hospital and of all patients hospitalized for disease in the Theater are presented. The inference can be drawn from this table that nearly half the patients with arthritis reaching a general hospital in the Theater were evacuated, another fourth being reclassified for limited service, and that the

TABLE 4 Average Number of Patients with Diseases Remaining in Peninsular Base Section Hospitals on a Given Day Each Month (March through November, 1944)

TYPE OF DISEASE	NO. OF CASES	PERCENTAGE OF TOTAL DISEASES	PERCENTAGE OF NONCOMMUNICABLE DISEASES
Noncommunicable			
Surgical	1,327	12.9	18.4
Neuropsychiatric	1,315	12.8	18.2
Liver and gall bladder	872	8.4	12.0
Skin	676	6.5	9.4
Arthritis	343	3.3	4.7
Other musculoskeletal	333	3.2	4.6
Genitourinary	298	2.9	4.1
Gastrointestinal	265	2.6	3.6
Ear	220	2.1	3.0
Eye	198	1.9	2.7
Cardiovascular	153	1.5	2.1
Dental	139	1.3	1.9
Allergic	81	0.8	1.1
Miscellaneous	1,032	10.0	14.2
Totals	7,252	70.4	
Communicable	3,119	29.6	
Grand total	10,371		

incidence of evacuation and reclassification was greater among arthritic patients than among the run of medical patients.

It was not possible to gather extensive data regarding the disposition of arthritic patients from other installations than general hospitals. However, many of the 235 soldiers with joint disease discharged from Fifth Army evacuation hospitals during August, 1944 (Table 1), returned to duty was not available, but an indication was furnished from the records of the Third Convalescent Hos-

genic rheumatism" are included in these figures, and the number of cases in this group, in addition to those in the arthralgia group, nearly equals the sum of the cases of definite arthritis.

Numerical data concerning the relative incidence of the various types of arthritis encountered in the Theater were available only from general hospitals. The impression gained, however, from conferences with medical officers in station and evacuation hospitals was that the patients with arthralgia made up by far the greatest proportion of those with joint symptoms. This opinion is reflected in the relatively large number of such patients in general hospitals, although in other installations many patients were returned to some form of duty and therefore never reached a general hospital. Figures from two British general hospitals in 1940, which were evidently acting chiefly as station hospitals

(unqualified) and about a fourth, muscular rheumatism or myositis.¹ Gonorrheal arthritis comprised about 12 per cent of the cases of arthritis tabulated in World War I, probably exceeding in incidence for reasons discussed below, this form of infectious arthritis in the Mediterranean Theater. Although there are variations in individual hospitals and in groups of hospitals, no significant difference in incidence in the Theater between rheumatoid and hypertrophic arthritis is discernible when the available figures are combined. In the two British general hospitals mentioned above, about twice as many patients with rheumatoid as with hypertrophic arthritis were tabulated² — a ratio confirmed in the United States by Kinsey,⁴ whose study, however, was concerned only with patients separated from the service for disability. Boland and Corr's⁵ results agree more nearly with those obtained in

TABLE 10 *Disposition of Patients with Arthritis on the Medical Service of the Twelfth General Hospital to December 1, 1944*

DIAGNOSIS	TOTAL CASES	DUTY		LIMITED SERVICE		EVACUATION	
		NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE
Arthritis	157	11	7.0	24	15.3	122	77.7
Rheumatoid	72	7	9.8	12	16.7	53	73.5
Hypertrophic	51	1	2.0	10	19.6	40	78.4
Other (chiefly infectious)	34	3	8.8	2	5.9	29	85.3
Arthralgia, myositis and myalgia	101	26	25.8	27	26.9	48	47.5
Psychogenic rheumatism	51	4	7.8	30	58.8	17	33.4
Totals	300	41		81		187	
Averages			13.3		26.2		60.5

at that time, are in agreement, several times as many cases being classified as "fibrositis" as those with real arthritis.² In a study by Boland and Corr⁵ of 450 consecutive cases diagnosed as arthritis or an allied organic condition before admission to the Medical Service of Hoff General Hospital, patients with rheumatoid or hypertrophic arthritis were outnumbered by those with psychogenic rheumatism. In this study the diagnosis of fibrositis was made infrequently, perhaps because of the care with which the authors investigated the possibility that emotional factors produced somatic symptoms in the musculoskeletal system. At the Army and Navy General Hospital at Hot Springs, Arkansas, the incidence of the various types of rheumatic disease based on 2000 consecutive admissions in 1944 was as follows: rheumatoid arthritis, 34.3 per cent, psychogenic rheumatism, 18.8 per cent, fibrositis, 13.6 per cent, hypertrophic arthritis, 12.4 per cent, gonorrheal arthritis, 1.4 per cent, and miscellaneous, 19.5 per cent.⁶ The criteria governing the admission of patients to this hospital are not available, but it is significant that cases of fibrositis and psychogenic rheumatism made up about a third of the total number. The figures for World War I show that about half of 65,192 soldiers admitted for joint disease were labeled arthritis

in the Mediterranean Theater, although a slightly greater number of cases of rheumatoid arthritis were found, and nearly three times as many patients with rheumatoid as with hypertrophic arthritis were admitted to the Army and Navy General Hospital.

In conclusion, since exact figures are not available, the relative incidence of the various types of arthritis encountered in the Theater may be summed up briefly. Patients with joint symptoms but without objective changes were encountered more frequently than those with any of the organic types of arthritis. In many of this group, a psychogenic origin of symptoms was demonstrated when sought for. Among those with real arthritis, no significant difference in incidence was demonstrated between the rheumatoid and the hypertrophic types. Cases of specific infectious arthritis were relatively infrequent. The distribution was roughly as follows: arthralgia, 40 per cent, rheumatoid and hypertrophic arthritis, 25 per cent each, and specific infectious arthritis, less than 10 per cent (Table 10). So far as prognosis for return to duty was concerned, patients with arthralgia presented a much more favorable outlook than those in either the rheumatoid or hypertrophic groups.

from the Army on certificates of disability for discharge in the last three months of 1942 at the Station Hospital, Camp Blanding, Florida. Patients with chronic arthritis made up 5 per cent of the total, and were outnumbered only by patients with psychoneurosis, duodenal ulcer and psychoses. In spite of such screening, which was probably

cases, although some have undoubtedly been included under fibrositis or variations of that term. For these reasons no exact information is available regarding the types of arthritis seen in the ten general hospitals, combined figures from which were obtained from answers to the questionnaire, but the large size of the arthralgia-myositis group, which

TABLE 8 Patients Evacuated from Mediterranean Base Section because of Disease (March-June, 1944)

DIAGNOSIS	NO OF CASES	PERCENTAGE	DIAGNOSIS	NO OF CASES	PERCENTAGE
Neuropsychiatric disorder	1513	59.0	Circulatory disorder	179	6.7
Psychoneurosis	699	27.4	Trench foot	55	2.1
Dementia praecox	427	16.4	Valvular heart disease	25	1.0
Psychosis	228	9.0	Other	99	3.6
Other	159	6.2			
Musculoskeletal disorder	254	10.0	Disease of eye, ear, nose and throat	92	3.6
Arthritis	128	5.0	Otitis media	26	1.0
Rheumatic fever	63	2.5	Other	66	2.6
Other	63	2.5			
Respiratory disease	210	8.2	Miscellaneous	123	4.8
Tuberculosis	88	3.0	Malaria	34	1.3
Asthma	49	2.4	Nephritis	32	1.2
Other	73	2.8	Dermatosis	23	1.0
Gastrointestinal disease	194	7.7	Other	34	1.3
Peptic ulcer	169	6.7			
Jaundice	15	0.6			
Other	10	0.4			

representative of the training camps in the United States, arthritis constituted, as shown by the data presented in this section, one of the important causes of disability in troops overseas.

TYPES OF ARTHRITIS

The "Index of Standard Diagnoses" generally used in Army hospitals did not, until amended, encourage an attempt at an exact diagnosis of the arthritides of unknown cause. Under Diagnosis

exceeded any of the others, is apparent (Table 9). The disposition of each type is also expressed in this table, although the figures are, of course, not of great significance on account of the groups with type unspecified. As might be expected, they show a trend toward return to duty in the acute and infectious groups and demonstrate clearly the more favorable outcome in the arthralgia group as compared to that in the cases of real arthritis.

Table 10 presents a classification of the patients

TABLE 9 Disposition of Patients with Arthritis in Ten General Hospitals to December 1, 1944 (as Obtained from Questionnaires)

DIAGNOSIS	TOTAL CASES	DUTY		LIMITED SERVICE		EVACUATION	
		NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE
Arthritis	2,020	418	20.7	429	21.2	1,173	58.1
Rheumatoid	393	85	21.3	44	11.2	264	67.5
Hypertrophic	621	66	10.6	170	27.4	385	62.0
Chronic (type unspecified)	787	177	22.5	189	24.0	421	53.5
Acute (type unspecified)	159	70	44.0	17	10.7	72	45.3
Other (chiefly infectious)	60	20	33.3	9	15.0	31	51.7
Arthralgia	497	242	48.6	187	37.6	68	13.8
Myositis, myalgia	421	296	70.2	76	18.0	49	11.8
Totals	2,938	956		692		1,290	
Averages			32.6		23.6		43.8

0750, the medical officer was not asked to specify whether he was dealing, for example, with rheumatoid or hypertrophic arthritis. In some hospitals, additional diagnoses were provided for this purpose, but in others any such subdivision was left to the initiative of the ward officer. The written questionnaire sent to general hospitals was drawn up with this point in mind, and headings were provided for both acute and chronic arthritis, type unspecified, as well as for rheumatoid and hypertrophic arthritis. Arthralgia, myositis and myalgia were believed to be the most frequent terms used for this group of

with arthritis discharged from the Medical Service of the Twelfth General Hospital. The opportunity was presented of examining the discharge summaries of all the patients enumerated and formulating an opinion concerning the correct diagnosis when the type of arthritis was unspecified or when the diagnosis seemed at variance with the facts available. The breakdown into types of arthritis was therefore revised and was not entirely in accord with the medical records or with the Army nomenclature. Owing to the completeness of the records of this hospital, a group of cases labeled "psycho-

Regarding physical examination, the consensus was that objective joint changes, chiefly swelling, were necessary for a definite diagnosis of rheumatoid arthritis involving the peripheral joints. One obvious exception to this rule occurred when swelling had previously been noted in the clinical record accompanying the patient in the process of evacuation. A careful check of the peripheral joint findings in the series of 132 patients with diagnoses of rheumatoid arthritis showed only 11 without evidence of articular swelling, 3 of whom had definite limitation of motion. The remainder fulfilled the diagnosis by characteristic symptomatology and by multiple and symmetrical joint involvement limited to tenderness and pain on motion. Another medical officer with a large experience in arthritis stated that he had also occasionally made the diagnosis of rheumatoid arthritis under these conditions. The tendency of the disease to be bilateral, often in a strikingly symmetrical fashion, is especially characteristic of rheumatoid arthritis. In this series of 132 cases, 87 per cent of patients with extraspinal involvement had at least one pair of corresponding joints affected. On the other hand, 12 cases were seen with entirely unilateral involvement of more than one joint, the duration in 6 averaging nearly ten years. One interesting finding by Boland,⁷ in a general hospital in the United States, was not confirmed. In 70 per cent of his 41 cases of rheumatoid arthritis, the involvement was confined to the lower extremities. A check of 112 patients with peripheral arthritis in the Mediterranean Theater disclosed that the upper extremities alone were involved in 15, the lower extremities in 22 and both in 75. Similarly, Boland found 41 per cent with metatarsophalangeal and toe involvement in contrast to 10 per cent with arthritis of corresponding joints of the hands, whereas a study of the 112 patients in the Theater revealed an involvement of 30 per cent and 53 per cent respectively.

Weight loss, cold, clammy extremities, tremor, muscle atrophy and weak grips were also detected on physical examination. Intis, which may be a manifestation of rheumatoid arthritis, or a history of this condition, was encountered in only 3 per cent of the series. Fever, with temperatures occasionally ranging as high as 102°F, was recorded in about a sixth of the patients. The incidence of splenomegaly, lymphadenopathy and rheumatoid nodules was much less than that usually observed in civilian practice, the nodules being found in only 5 per cent of patients with peripheral joint involvement. This difference was probably associated with the relative mildness of the disease: an estimate of the total severity in the series at the Sixth General Hospital showed the cases to be mild in 33 per cent, moderate in 60 per cent and severe in only 7 per cent.

Although no specific laboratory test for rheumatoid arthritis is known, the sedimentation rate has been found helpful diagnostically, chiefly in a con-

firmatory sense, and although it is recognized in civilian practice that a patient may have rheumatoid arthritis and a normal sedimentation rate, this group has been small and probably numbers less than 10 per cent. From examination of the case records at the Sixth and Twelfth general hospitals, the reverse was true. The rate was increased in only 52 per cent of 112 patients in the former series, and in 36 per cent of 52 patients on whom the test was performed in the latter. The difference may result from the more advanced type of case seen in civilian hospitals or because more accurate procedures, such as the Rourke-Ernstene method, have been employed than those generally used in Army laboratories (Wintrobe and Westergren). The white-cell count was variable and not of diagnostic importance and few patients in the Theater showed an anemia consequent to the disease. It was generally agreed in the Theater that articular x-ray examination usually proved negative except in cases of rheumatoid spondylitis. In the Twelfth General Hospital only about a sixth of the patients with peripheral joint involvement showed changes (with the exception of soft-tissue swelling), whereas in the Sixth General Hospital 30 per cent evidenced varying degrees of bony atrophy and another 8 per cent, joint narrowing or destruction. The conclusion can thus be drawn that the diagnosis of rheumatoid arthritis in the stage usually encountered in the Theater generally had to be established by the clinical picture rather than by laboratory or x-ray study.

Differential Diagnosis

The majority of observers in the Theater stated that rheumatic fever was readily distinguished from rheumatoid arthritis. Acute types of rheumatoid arthritis, however, as well as rheumatic fever tending toward long-continued joint involvement, at times furnished difficulty. Usually the distinction between the two diseases could be made after several weeks' observation, but in any event, the indications for treatment and disposition were similar, irrespective of the final diagnosis. Hypertrophic arthritis was ordinarily easily differentiated from rheumatoid arthritis. Exceptions occasionally occurred in patients with hypertrophic arthritis showing a marked degree of synovitis and in those, usually in the older age groups, who had rheumatoid arthritis clinically but demonstrated hypertrophic changes on x-ray study. The distinction between rheumatoid arthritis and the conditions grouped under the heading of arthralgia proved especially difficult, even in cases in which the localization was apparently extra-articular. In general, the presence or absence of objective joint changes constituted the deciding factor, since, as mentioned above, the diagnosis of rheumatoid arthritis was rarely made in their absence. The sedimentation rate and x-ray examination were not of great value in this type of case,

RHEUMATOID ARTHRITIS

In this paper no attempt is made to present an inclusive description of rheumatoid arthritis derived from the literature or from observations in civilian practice. Instead, the more important aspects of the disease as seen in the Mediterranean Theater will be outlined, comparison being made, when indicated, with civilian experience. The name "rheumatoid arthritis" is used throughout, both for the sake of uniformity and because it was generally, if not universally, employed in the Theater. Rheumatoid spondylitis, although believed to be a variation of rheumatoid arthritis rather than an independent entity, and atypical forms are chiefly discussed for greater convenience in separate sections.

The age distribution in 132 consecutive cases of rheumatoid arthritis personally studied is presented in Table 11. About 75 per cent of patients were

TABLE 11 Age Distribution of 132 Patients* with Rheumatoid Arthritis Studied in the Sixth General Hospital

AGE GROUP	NO. OF CASES	PERCENTAGE
15-19	0	0.0
20-24	29	22.0
25-29	30	22.8
30-34	39	29.5
35-39	18	13.6
40-44	11	8.3
45-49	5	3.8
50-54	0	0.0

*Mean age 30.8 years

from twenty to thirty-four years of age, and the mean age was thirty years and nine months. Since the age distribution of the troops involved is not known, these figures give no clue regarding a predilection of the disease for any age group. A comparison may be made, however, with the mean age of thirty-four years and nine months in 101 cases of arthralgia and thirty-eight years and ten months in 51 cases with hypertrophic arthritis, both series having been obtained from the records of the Twelfth General Hospital.

That the cause of rheumatoid arthritis is not yet known may be stated without further discussion. Precipitating factors in civilian series have been found to be infections (especially of the upper respiratory tract), trauma, exposure to cold and dampness and emotional stress. Such factors were elicited in a minority of the patients with an onset recent enough to make the history reliable. Nearly half the 132 patients in the series, however, definitely dated the onset of the arthritis or noted an exacerbation in a previously existent disease within two months following their landing in North Africa. These findings are difficult to evaluate but suggest a possible association of the course of the disease with the hardships and anxieties of overseas service

or the unfavorable climatic conditions of the winter of 1942-1943.

Diagnosis and Clinical Features

There is no specific diagnostic test for rheumatoid arthritis, but the disease must be considered an entity, since both the clinical picture and the roentgenologic and pathological findings are unmistakable in advanced cases. Such patients, of course, with the exception of those with spondylitis, rarely escaped the screening process of induction and preliminary training and were only occasionally encountered in the Theater. The diagnosis of the disease under such conditions depended on the demonstration of a fairly characteristic total clinical picture, in addition to the exclusion of other forms of organic or functional joint disease. So far as the history is concerned, an inquiry into the previous existence or past attacks of joint disease is of primary importance. In the series of 132 patients, slightly over half gave a definite history of symptoms consistent with rheumatoid arthritis before induction and about two thirds gave evidence of the disease before arrival in North Africa. The disease had obviously started five to ten years previously in many cases and twenty years or more before admission in 5 patients. A history of previous attacks lasting from a few weeks to several months was usual (although about a third of the patients were in their first attack of less than a year's duration). The majority of patients who had had earlier attacks had never enjoyed a complete remission but continued to have morning stiffness and articular pains of varying severity but evidently insufficient to prevent induction and embarkation. As in civilian practice, the preceding attacks had often been erroneously labeled inflammatory rheumatism or rheumatic fever.

In the diagnosis of rheumatoid arthritis, it is essential to recall that one is dealing with a generalized disease exhibiting well marked constitutional manifestations. A history of easy fatigability, anorexia or weight loss was obtained in 87 per cent of cases in the Sixth General Hospital series, sometimes before the actual onset of arthritis. These symptoms, one or more of which could, of course, have been elicited from a large proportion of the soldiers in the Theater, were of less diagnostic value than in civilian practice, unless of a severe degree. Vasomotor instability, evidenced by cold extremities, often with increased sweating, was found in about two thirds of the patients in the series, and an equal number had numbness of the hands or feet, with paresthesias variously described as tingling, burning or stinging. Motor weakness, especially of the grips, and tremor were additional neurologic symptoms. Since many patients with rheumatoid arthritis had minimal articular signs, the presence of the symptoms listed above was of real diagnostic assistance.

rheumatoid arthritis. The diagnosis is established by the ruling out of specific infectious arthritis or gouty arthritis and by the later development of unmistakable rheumatoid arthritis.

This form was generally recognized in the Theater and comprised 18 per cent of cases with peripheral joint involvement in the series. The diagnosis was made under a varying terminology in addition to rheumatoid arthritis, but usually as "arthritis, infectious, cause undetermined." Proper emphasis was laid on the importance of eliminating a specific infectious arthritis by means of culture of the synovial fluid and examinations for genitourinary gonorrhea. A therapeutic test with chemotherapy was also a frequent procedure — in fact routine in some hospitals — but usually without definite effect on the course of the arthritis. Nevertheless, this condition tended to subside gradually, irrespective of treatment, and often went into a complete remission. If a remission took place, it seemed reasonable to discharge the patient to limited service or to duty in the Zone of Communications.

RHEUMATOID SPONDYLITIS

Since this variety of rheumatoid arthritis affects males about ten times as often as females and since its onset is most frequent in the second and third decades of life, a relatively large number of cases was expected in soldiers. This expectation has been fulfilled, according to available reports in the literature, the spinal type even outnumbering the peripheral type of rheumatoid arthritis in a British Army series and comprising 37 per cent of 89 patients with rheumatoid arthritis in a general hospital in the United States.⁵ In the Mediterranean Theater the incidence was not so high, averaging 20 per cent of patients with rheumatoid arthritis at the Sixth General Hospital but lower in the records of other hospitals, where the condition was not especially looked for and was not always recognized when present. The diagnosis of rheumatoid spondylitis was made clinically with certitude in advanced cases with nearly rigid spines and later confirmed by the characteristic x-ray appearance of the sacroiliac joints. In earlier cases, it was confused at first with various types of organic and functional low-back conditions, and the diagnosis again was made by the bilateral, destructive changes seen in roentgenograms of the sacroiliac joints. A few cases were noted with the clinical picture of rheumatoid spondylitis, including marked constitutional symptoms, but with repeatedly negative x-ray examinations. In these patients, a presumptive diagnosis of rheumatoid spondylitis was made, without the opportunity of confirmation, since the symptoms were severe enough to warrant evacuation.

On account of the frequency of rheumatoid spondylitis in soldiers, x-ray examination of the lower back with careful interpretation of the sacroiliac joints seemed indicated in every patient with

persistent back symptoms. In two small series examined in the Theater, 5 per cent and 10 per cent of patients, respectively, were found to have this condition, whereas in 181 cases with back complaints studied in a general hospital in the United States, 33, or 18.7 per cent, warranted a diagnosis of rheumatoid spondylitis.⁶ The extent of the x-ray findings often seemed out of all proportion to the duration of the symptoms and the degree of disability. Not a few soldiers with advanced changes on x-ray examination fought through a campaign, including a parachutist who had made a number of jumps.

SUMMARY

The general incidence of arthritis among American troops hospitalized for disease in the Mediterranean Theater was estimated to be relatively low (about 3 per cent), but approximately 275,000 man-days were lost for this reason from January, 1943, through April, 1945. As a source of permanent loss of man power from the Theater by evacuation or from combat troops by reclassification, arthritis was highly important.

Patients without objective evidence of joint disease nearly equaled in incidence those with evident arthritis. In general hospitals, the distribution was estimated as 40 per cent for arthralgia and psychogenic rheumatism, 25 per cent each for rheumatoid and hypertrophic arthritis and less than 10 per cent for specific infectious arthritis.

The onset of rheumatoid arthritis or an exacerbation was frequently noted following arrival overseas. A history of arthritis prior to induction was given in about half the cases, and before embarkation in about two thirds. Helpful points in diagnosis were a history of constitutional, vasomotor and neurologic symptoms and a finding of symmetrical joint involvement. The diagnosis of rheumatoid spondylitis was made in about a fifth of the patients with rheumatoid arthritis. Laboratory tests, including the sedimentation rate, and x-ray films were not of primary diagnostic value. The total severity of the disease was generally less than that noted in civilian hospitals. Difficulty was experienced in the differential diagnosis of arthralgia and psychogenic rheumatism. An attempt at treatment was made only in milder cases considered susceptible to remission. Only 20 per cent of patients with rheumatoid arthritis were returned to duty.

REFERENCES

1. *The Medical Department of the United States Army in the World War*. 17 vol. Washington: Government Printing Office, 1929.
2. Hench P. S., Osgood R. B. and Wainwright, C. W. Outline of diagnosis and treatment of common rheumatic diseases. *Army M. Bull.* 60:1-23, 1942.
3. Overstreet S. A. and Yeatts H. B. Experience of medical division of U. S. Naval Base Hospital No. — for its first year of operation. *Mil. Surgeon* 95:441-446, 1944.
4. Kinsey, R. E. Study of 1000 cases separated from Army on certificate of disability for discharge. *Bull. U. S. Army M. Dept.* 69:64-75, 1943.
5. Boland E. W. and Corr W. P. Psychogenic rheumatism. *J. A. M. A.* 123:805-809, 1943.
6. Bauer W. Personal communication.
7. Boland E. W. Arthritis and allied conditions in Army general hospital. *California & West. Med.* 60:7-9, 1944.

except as a check on the clinical impression. Daily questioning of the patient, with careful examination of painful joints over a period of several weeks, often clarified the decision. When doubt finally existed and the patient's course remained stationary, the tendency was to abandon the diagnosis of rheumatoid arthritis for the time being and to return the soldier to some form of duty. In any patient with articular complaints without objective findings, the possibility of so-called "psychogenic rheumatism" was of course strongly suspected, and an attempt made to establish the presence of an underlying neurosis. Further details will be presented in a subsequent paper. Cases of traumatic arthritis were usually readily separated from those of rheumatoid arthritis except in the knee, where the physical finding of a dislocated meniscus or other injury was occasionally simulated by rheumatoid arthritis involving the joint. In such cases diagnostic joint aspirations and examination of the synovial fluid were apparently not utilized often enough. In certain patients in whom the joints of the feet were involved by rheumatoid arthritis, a diagnosis of foot strain was erroneously made at first.

Treatment

No specific treatment for rheumatoid arthritis has as yet been found, and none of those claimed to be specific without convincing evidence were tried in the Theater, including parenteral injection of gold compounds, massive doses of vitamin D and the use of autogenous or stock vaccines. A few patients were given fever therapy, usually with intravenous typhoid vaccine, without lasting beneficial results. Opinion was divided regarding the removal of focal infection. In a few hospitals, a rather thorough check for foci of infection was made. The results of removal or treatment of supposed foci were disappointing on the whole, although successes were reported in a few cases. In most patients, only obvious foci were removed—for example, the tonsils when the onset of the arthritis followed an acute tonsillitis or certain teeth when marked dental sepsis was present. Again, success in influencing the course of the disease was seldom attained. In well marked cases or those of long standing, the tendency was to evacuate the patient without an attempt at more than palliative treatment. In milder cases, especially those with early, acute involvement of one or a few joints, hospitalization was maintained until the patient could be returned to some form of duty or the chances of a remission seemed remote. Such patients were given general treatment, including bed rest, relief of pain and physical therapy, and were usually examined for focal infection.

Disposition

A compilation from ten general hospitals, with the elimination of those receiving many patients

from other general hospitals for evacuation, revealed that about a fifth of the patients with the diagnosis of rheumatoid arthritis returned to full duty, the large majority of the remainder being evacuated to the Zone of the Interior (Table 9). The policies that governed this distribution may be summarized as follows. It was generally agreed that only an occasional patient merited a return to full duty, including those in their first acute attack with apparent complete subsidence and those of mild severity with duties that lent themselves to favorable living conditions, opportunities for rest and a chance for medical supervision. Some of the records examined, however, indicated that these conditions were not entirely fulfilled, and that further hospitalization would be necessary. Essentially the same conditions were laid down for limited service, except that a few hospitals determined this disposition more on the patient's ability to perform some kind of duty at the time of discharge than on the probability of his being able to continue a particular task. That more advanced cases and milder cases with repeated hospitalization should be evacuated was universally recognized—a fact that accounts for the high proportion of such dispositions.

Owing to the variability of the course of rheumatoid arthritis, it seems impossible to lay down rules for disposition that would finally prove applicable to every case encountered in overseas service. When the diagnosis is still in doubt, the soldier should certainly be returned to whatever duty he can perform at the time. But since the disease bears a definite threat of chronicity and long-standing disability, evacuation to the Zone of the Interior should provide the best chance for a relatively favorable outcome once the diagnosis has been established. Certainly, the hardships and anxieties of overseas service are likely to have a deleterious effect on the progress of the disease. Furthermore, it is not to the best interests of the service to return a man to duty who bears the liability or even probability of recurrence. From these considerations, although no figures for such recurrences are available, it is believed that, as with peptic ulcer and active pulmonary tuberculosis, evacuation is indicated in all but a few selected cases.

ATYPICAL RHEUMATOID ARTHRITIS

Although rarer than the usual form of rheumatoid arthritis, an atypical form has been clearly defined in civilian practice. This variety appears acutely and at times follows a definite infection, usually of the upper respiratory tract. It is characterized by severe inflammation of one or a few joints in an asymmetrical fashion and may be accompanied by fever. Foci of infection of presumed etiologic significance are sometimes found, but any direct beneficial result from their removal is open to question, since remissions are more frequent and complete in this type than in the usual varieties of

patients were between the ages of fifty-one and sixty years, 14 were in the seventh and 11 in the fifth decades. Thirty-three of the 52 patients were men, and 19 were women.

The surgical procedures are presented in Table 1. Extensive operations were performed on the stomach in 5 cases and on the large bowel—including a Miles or Mikulicz resection, colectomy and colostomy—in 19. Eight patients had pelvic operations, and if these are combined with the 19 cases in which surgery of the colon was performed, a group of 27 cases is formed, confirming the well known fact that thrombosis and embolism are likely to follow

TABLE 1 *Surgical Procedures Employed*

OPERATION	No. of Cases
Miles resection (for carcinoma of rectum)	8
Mikulicz resection (for carcinoma of sigmoid)	6
Cholecystectomy	3
Transverse ileocolostomy (carcinoma of transverse colon)	2
Repair of uterine and rectal prolapse	2
Pancreatotomy	2
Gastroenterostomy and cholecystostomy	1
Mikulicz resection of terminal ileum, cecum and hepatic flexure	1
First stage Lahey resection (for carcinoma of rectum)	1
Splenectomy and total gastrectomy	1
Colectomy	1
Subtotal gastrectomy	1
Gastrostomy	1
Resection of carcinoma of sigmoid (excision of involved loop and side-to-side anastomosis)	1
Cecostomy	1
Right pneumonectomy	1
Craniotomy (for brain tumor)	1
Suprapubic prostatectomy	1
Thoracotomy (for lung abscess)	1
Vesical diverticulectomy	1
Nephrectomy and ureterectomy	1
Synovectomy and revision of knee joint	1
Resection of frontal lobe	1
Bilateral oophorectomy	1
First-stage splanchicectomy	1
Cervical laminectomy	1
Supraorbital neurectomy	1
Pyelotomy	1
Repair of diaphragmatic hernia and splenectomy	1
Exploratory laparotomy	1
Total	48

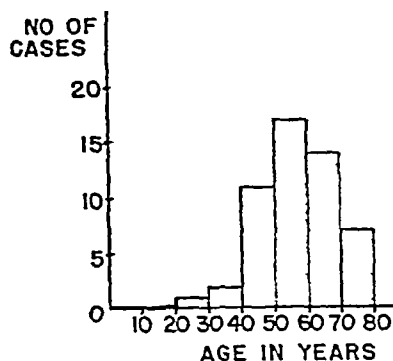
operations in the pelvis. Cranial operations in 3 cases and splanchicectomy in 1 case were followed by fatal pulmonary embolism.

It has long been recognized that a history of previous vein trouble may predispose to venous thrombosis. Of 11 patients (22 per cent), 8 had varicose veins, and 3 a history of phlebitis. In 9 (17 per cent), no mention was made in the history of any previous vein trouble. This is a point in examination that should be most diligently sought for, as emphasized below.

The occurrence of postoperative pulmonary embolism according to the time elapsed after operation is summarized in Table 2. The period of greatest liability to the first pulmonary embolism was the sixth to the sixteenth postoperative day, 25 patients falling in this group. The first pulmonary embolus occurred before the sixth postoperative day in 11 cases and after the sixteenth day in 12.

The signs and symptoms associated with pulmonary embolism in the 52 cases are recorded in Table 3. Sagall, Bornstein and Wolff⁵ pointed out

that the clinical course of pulmonary embolism is punctuated by a series of events in which numerous signs or symptoms may be present. In the intervals there may be a complete absence of signs or complaints. It is further stated that on clinico-

FIGURE 1 *Incidence of Death due to Pulmonary Embolism according to Age*

pathological grounds each episode does not necessarily connote a separate pulmonary embolism. One embolus may be associated with several clinical episodes, and conversely, more pulmonary infarcts may be found at autopsy than can be accounted for clinically. The table demonstrates the frequency of elevated temperature, circulatory collapse, dyspnea, tachycardia, cyanosis and chest pain in thromboembolic disease. Chest pain, cyanosis and circulatory collapse have long been considered the earmarks of pulmonary embolism but they are only the most dramatic—not the most frequent—signs. Elevated temperature and tachycardia preceding the onset of dramatic symptoms are far more important warning signs.

The 52 cases were divided into three categories according to the time of death after the first symptoms of pulmonary embolism had been noticed.

TABLE 2 *Occurrence of Pulmonary Embolism according to Postoperative Day*

POSTOPERATIVE DAY	No. of Cases
1	1
2-5	10
6-10	15
11-15	12
16-20	7
21-25	2
26-37	3

This was done to determine if warning signs or symptoms were present, affording the clinician time to adopt preventive measures. Group 1 includes the sudden deaths or patients who died within an hour of the onset of pulmonary embolism, 22 cases (42 per cent) comprise this category. Group 2 was composed of patients who died within two to twenty-four hours after the first known pulmonary

THE PREVENTION OF POSTOPERATIVE PULMONARY EMBOLISM*

An Analysis of Fifty-Two Fatal Cases in Six Years

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INTEREST in venous thrombosis and pulmonary embolism has received great impetus in the past eight years by the simultaneous development of two methods of treatment — namely, venous section and ligation and anticoagulant therapy by heparin or dicumarol or by a combination of these anticoagulants. Unfortunately, in many minds the two methods have become competitive, whereas they should be complementary. There are definite indications for both procedures. It is readily conceivable that in many hospitals where adequate laboratory and clinical experience in the use of dicumarol is lacking, a precise and absolute control of the situation by femoral ligation is the method of choice. With more and more confidence, however, afforded by experience with anticoagulant therapy and statistical support from other workers in this field, in addition to our own, femoral ligations at the Lahey Clinic are, with few exceptions, limited to patients with venous thrombosis who must soon have a second-stage operation, to those with conditions such as hemorrhagic colitis in which an anticoagulant effect would be dangerous, to those with poor liver function and to those with ambulatory recurrence of phlebothrombosis with pulmonary embolism. If there is any hint of venous thrombosis, the present method of anticoagulant therapy is to start immediately with both heparin in Pitkin's menstruum and dicumarol. A single dose of heparin in Pitkin's menstruum prolongs the coagulation time before two hours have passed and protects the patient until a two-day latent period of dicumarol action has elapsed, by which time the prothrombin content has usually dropped. In the rare patient who is resistant to dicumarol the injections of heparin are continued every second day.

In the four years between January 1, 1942, and January 1, 1946, anticoagulant therapy was administered to 127 patients with postoperative venous thrombosis, with or without benign pulmonary embolism, with death in only 2. One patient had bilateral femoral vein ligation and only one dose of dicumarol. The other received inadequate doses of dicumarol and never obtained a prothrombin level within the therapeutic range, he was also given a transfusion, which destroyed the slight effect of the dicumarol, and died of a second pulmonary embolism a few hours later. After January 1, 1946, another

fatal case occurred in a patient with postoperative phlebothrombosis treated by anticoagulant therapy. He had been extremely ill with peritonitis but later had a septic infarct in spite of adequate prothrombin reduction. This infarct ruptured and caused terminal pneumothorax and empyema.

Such a record, together with the experience of Barker¹ with dicumarol and of Loewe, Rosenblatt and Hirsch² with heparin in Pitkin's menstruum, compares favorably with reports of the prevention of pulmonary embolism by venous ligation and section.^{3,4}

These results represent a great advance in the prevention of pulmonary embolism once a warning venous accident has occurred in the form of venous thrombosis or a benign pulmonary embolism. In spite of this advance, death may occur from sudden or unrecognized pulmonary embolism — a situation that must be met by prophylaxis, which is still an important factor in any consideration of postoperative pulmonary infarct. We have therefore attempted to analyze 52 sudden, unrecognized or untreated fatal cases of pulmonary embolism in an effort to ascertain ways and means to reduce the mortality further. These deaths occurred from 1940 to 1946. Forty-eight of the fatal cases were postoperative among approximately 45,000 major surgical operations. In only 2 cases had thrombosis and embolism been recognized and the patient treated after a warning pulmonary embolism, as described above. Two deaths occurred in medical cardiac cases, and 1 patient died before contemplated surgery. Autopsy was performed in 21 cases. The remaining 31 patients gave ample clinical evidence of pulmonary embolism.

That prophylactic exercises are an important factor in the prevention of pulmonary embolism is suggested by a comparison of the number of deaths from pulmonary embolism in a year in two hospitals, in one of which bicycle exercises were faithfully supervised by the nursing staff, and in the other of which these measures had not yet been generally enforced, in the latter there were three times as many deaths from pulmonary embolism as in the former. Because of these figures, we now advocate wiggling of the feet a thousand times a day as being universally and immediately applicable to all types of surgical patients.

Figure 1 illustrates the incidence of death from pulmonary emboli according to age. The greatest incidence occurred in the sixth decade. Seventeen

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pected mass in the right lung. In the four days between the time he was first seen and his entry into the hospital, a mild superficial bilateral thrombophlebitis had developed, for which ace bandages were applied. Two weeks later a right pneumonectomy was performed. On the seventh day after operation a low-grade fever developed, and on the eighth day the patient complained of soreness in the thighs along the course of both saphenous veins, the latter subsided in three days, but a mild non-productive cough developed. On the sixteenth postoperative day, after being up for two days, he was suddenly stricken with dyspnea and cyanosis. Roentgenologic examination confirmed a clinical diagnosis of pulmonary infarct. While arrangements for a bilateral femoral ligation were being

TABLE 6 *Warning Signs in Patients Dying over Twenty-four Hours after Onset of Pulmonary Embolism*

SIGN OR SIGNS	AVERAGE DURATION	NO OF CASES	CASES WITH HISTORY OF VENOUS TROUBLE
	days		
Phlebothrombosis and benign pulmonary embolism following coronary occlusion	7	1	1 (superficial phlebitis)
Phlebothrombosis and benign pulmonary embolism (1 patient treated*)	24	2	—
Multiple pulmonary emboli, positive electrocardiographic and x ray findings, fever and chest pain	8	1	—
Fever and multiple lung abscesses	7	1	—
Benign pulmonary embolism (mistaken for postoperative atelectasis)	8	1	—
Fever, tachycardia, dyspnea and shock	4	2	—
Fever, benign pulmonary embolism and positive x ray findings	4	1	1 (varicose veins)
Fever and benign pulmonary embolism	5	1	—
Totals		10	2

*Warning signs recognized after two days, but treatment not given because the patient had a hopeless cancer

†Electrocardiogram positive for cor pulmonale

made, he suddenly became cyanotic, gasped for breath and died. Post-mortem examination revealed pulmonary embolism as the direct cause of death.

Group 3 included 10 cases (Table 6). The actual interval between the benign and the fatal embolism was one to twenty-four days. It is in this group that the most time naturally occurred for the institution of active therapeutic measures if warning signs and symptoms had been properly heeded. Two of the 10 patients gave a previous history of vein trouble, one having had varicose veins, and the other a superficial phlebitis. A third patient was not treated because of a hopeless carcinoma. A fourth patient was treated inadequately by anticoagulant therapy (the second patient treated in the entire group of 52 cases).

This patient was a sixty-two-year-old man who was admitted to the hospital in 1943 for a contemplated nephrectomy for carcinoma of the kidney. On admission, he gave evidence of a bilateral phlebothrombosis and benign pulmonary embolism. Bilateral femoral ligation was performed, and only

one dose (200 mg.) of dicumarol was given. Later that day there was hemorrhage from the right femoral ligation. The vein was retied, and the anticoagulant therapy discontinued. The prothrombin time never dropped to a bleeding level, much less to the therapeutic anticoagulant level. Pulmonary

TABLE 7 *State of the Legs Postoperatively in 48 Surgical Cases*

GROUP OF CASES	POSTOPERATIVE EXAMINATION OF LEGS NO MENTION	POSITIVE FINDINGS	NEGATIVE FINDINGS
1 (death in 1 hour)	14	0	8
2 (death in 2-24 hours)	6	3	9
3 (death over 24 hours)	5	2	1
Totals	25	5	18

sepsis developed, and the patient died two weeks later of a second pulmonary embolism. Autopsy showed old and recent pulmonary emboli and thrombi in the iliac veins but none in the inferior vena cava. Later experiences indicate that this patient might have been saved by either ligation of the inferior vena cava or energetic anticoagulant therapy.

Another patient in Group 3 whose history points a moral was a fifty-nine-year-old woman on whom a cholecystectomy was performed in 1940. On the thirteenth postoperative day she complained of pain in the left lower chest that was aggravated by breathing, a diagnosis of pulmonary infarction was made. The temperature rose to 100°F on the day before the infarction occurred and continued at that level until the eighteenth postoperative day, when the patient suddenly died while being given a bed bath. There was no note in the record of any leg examination postoperatively. In 1940 the treatment of choice would have been femoral-vein ligation.

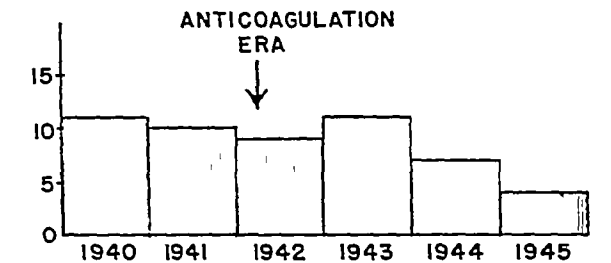


FIGURE 2 *Incidence of Death due to Pulmonary Embolism according to Year*

tion if the legs had shown any evidence of thrombosis. At present, the legs would be routinely examined in the presence of postoperative fever, and anticoagulant therapy begun.

Routine postoperative examination of the legs for evidence of phlebothrombosis should be carried out after all major surgical operations. This should

incident (20 cases, or 38 per cent) Group 3 consisted of patients who died over twenty-four hours after the first signs of thrombosis and embolism (10 cases, or 19 per cent)

From the point of view of treatment, it might be assumed that the patients in Group 1 could not have been saved once the pulmonary embolism had

TABLE 3 Signs and Symptoms Associated with Pulmonary Embolism in 52 Cases

SIGN OR SYMPTOM	No. OF CASES
Elevated temperature	37
Circulatory collapse	31
Dyspnea	30
Tachycardia	24
Cyanosis	24
Chest pain	12
Disorientation	6
Physical signs in chest	5
Coma	4
Hemoptysis	3
Positive roentgenologic findings	3
Positive electrocardiographic findings	2
Epigastric pain	2
Cough	1
Nausea	1
Vomiting	1
Pain in back	1
Pain in groin	1
Weakness	1
Incontinence	1
Dilatation of pupil	1
Convulsions	1

occurred. A careful analysis of the record, however, disclosed the interesting facts presented in Table 4. In 16 of the 22 patients there was ample warning before death to permit adequate prophylaxis, in the form of venous ligation or anticoagulant treatment. Fever or tachycardia, or both, had been present in

TABLE 4 Warning Signs in Patients Dying One Hour after Onset of Pulmonary Embolism

SIGN OR SIGNS	AVERAGE DURATION days	No. OF CASES	CASES WITH HISTORY OF VENOUS TROUBLE
Fever	7	11	2 (varicose veins)
Fever and tachycardia	7	4	—
Fever, tachycardia and mental confusion	3	1	—
None	—	6	3 (varicose veins)
Totals		22	5

15 of these cases for an average of seven days before death. The last patient had fever, tachycardia and mental confusion for three days prior to the fatal pulmonary embolism. Of 5 patients in this category who had a history of varicose veins, 3 died without any warning in the hospital. This leaves only 3 of the 22 cases in which there were no warning signs or history of previous vein trouble.

Of the 20 patients in Group 2, warning signs of thrombotic processes were present in 18 (Table 5). Fever alone or in combination with one or more other signs occurred in these patients from four to seventeen days before the onset of the first known pulmonary episode. In addition, 2 patients gave a

history of previous superficial phlebitis, and 2 had varicose veins. Only 2 in this group of 20 patients gave no premonitory signs or history of previous vein trouble.

It is instructive to review briefly the course of 2 patients in Group 2. One patient, a forty-seven-year-old woman, underwent an anterior gastroenterostomy, enteroenterostomy and cholecystectomy. On the fourteenth postoperative day superficial thrombophlebitis of the right leg developed. On the twenty-second postoperative day a deep venous thrombosis was detected in the left leg. She was then belatedly given dicumarol on successive days in doses of 200, 200, 100, 0, 100, 100, 0, 0, 0, 100 and 100 mg. She was allowed to dangle her feet out of bed on the twelfth day of anticoagulant therapy. Furthermore, a transfusion, which neutralized what anticoagulant effect might have been present, was administered for supportive

TABLE 5 Warning Signs in Patients Dying within Two to Twenty-four Hours of Onset of Pulmonary Embolism.

SIGN OR SIGNS	AVERAGE DURATION days	No. OF CASES	CASES WITH HISTORY OF VENOUS TROUBLE
Fever	4	1	—
Fever and tachycardia	6	7	1 (varicose veins)
Fever and venous thrombosis	8	1	1 (superficial phlebitis)
Fever and venous thrombosis, warning embolism and electrocardiographic changes	17	1	—
Fever, cyanosis and dyspnea	4	2	1 (varicose veins)
Fever and chest pain	6	3	—
Tachycardia alone	10	2	—
Disorientation	14	1	—
Fever and abdominal pain	6	2	1 (superficial phlebitis)
None	—	2	—
Totals		20	4

reasons that evening. The patient spent a confused night and died suddenly on the following morning. The prothrombin times during the course of treatment were 72, 100, more than 100, 105, 69, 85, 63, 105 and 100 per cent of normal. Since the patient had a so-called "therapeutic level" (below 65 per cent of normal) on only one day, the dosage schedule was obviously inadequate. Moreover, on the day the transfusion was given, the prothrombin time was 100 per cent of normal. The occurrence in rapid succession of thrombotic processes in both legs that occurred in this case supports the present practice of doing bilateral vein ligations even when the veins of only one extremity are clinically involved. Furthermore, the failure of dicumarol in rare cases to produce an adequate fall of the prothrombin percentage is a definite indication for venous ligation or persistence in the administration of heparin in Pitkin's menstruum.

The other case that stands out in this group from the viewpoint of prevention is that of a forty-two-year-old man who entered the hospital for a

cent of the deaths occurred after extensive pelvic or lower abdominal surgery, or both. This poses the question of routine prophylactic administration of heparin in Pitkin's menstruum and dicumarol shortly after such major surgical procedures.

The variability of the signs and symptoms associated with pulmonary embolism emphasizes the fact that a thrombotic process should be suspected postoperatively in every case of fever or tachycardia, or both.

Fifty-two per cent of the initial pulmonary emboli occurred between the sixth and sixteenth postoperative days, although a sufficient number occurred before and after that period to make one continuously on the alert for trouble.

Routine, careful examination of the legs postoperatively is required for evidence of phlebotrombosis.

Complete co-operation between the surgeon and the internist is essential to adequate therapy,

whether it consists of anticoagulants or surgical ligation of the veins.

In 85 per cent of the 52 fatal cases, some preventive measure was indicated by premonitory signs, usually in the form of elevated temperature or tachycardia, or both, occurring a sufficient time before the fatal embolism to allow adequate therapy to be administered.

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REFERENCES

- 1 Barker, N. W., Cromer, H. E., Hurn, M. and Waugh, J. M. Use of dicumarol in prevention of postoperative thrombosis and embolism with special reference to dosage and safe administration. *Surgery* 17:207-217, 1945.
- 2 Loewe, L., Rosenblatt, P. and Hirsch, E. Venous thromboembolic disease. *J. A. M. A.* 130:386-393, 1946.
- 3 O'Neil, E. E. Ligation of inferior vena cava in prevention and treatment of pulmonary embolism. *New Eng. J. Med.* 232:641-646, 1945.
- 4 Gaston, E. A. and Folsom, H. Ligation of inferior vena cava for prevention of pulmonary embolism: report of two cases. *New Eng. J. Med.* 233:229-233, 1945.
- 5 Sagall, E. L., Bornstein, J. and Wolff, L. Clinical syndrome in patients with pulmonary embolism. *Arch. Int. Med.* 76:234-238, 1945.

NEUROPATHIC FOOT LESIONS IN DIABETES MELLITUS*

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JOINT changes associated with diseases of the central nervous system were first described by Charcot. At first these changes were considered peculiar to tabes dorsalis and syringomyelia, but with extensive use of x-ray examination, similar changes have been found in other conditions. Leprosy may produce a similar picture, as may injury to a peripheral nerve, as described by Weinberg¹ in soldiers injured in World War I. Bone lesions similar to those in Charcot's joints have also been reported in association with diabetes mellitus.²⁻⁷

This report deals with neuropathic foot lesions that occur in patients with diabetes mellitus and are attributed to the effect of the diabetes on the nervous system. Seventeen cases of neuropathic foot lesions have been detected among approximately 20,000 consecutive cases of diabetes—an incidence of 1/1100. Additional cases have probably escaped recognition.

The earliest gross change detected in the foot with a diabetic neuropathic lesion is a unilateral or bilateral thickening of the tarsal region. No fluid is present in the joint. The swelling is painless, and no redness of the skin, heat or other signs of inflammation are present. These changes progress slowly and usually result in a thickened, deformed foot

with a tendency to eversion and external rotation and a flattening of the longitudinal arch.

On roentgenologic examination the neuropathic foot is similar to the chronic Charcot joint of syphilis except that the destruction is chiefly limited to the



FIGURE 1 Case 5

This x-ray film of the right foot shows destruction of the forward end of the astragalus and of most of the other tarsal bones with soft-tissue swelling.

tarsal and proximal ends of the metatarsal bones. The phalanges may also atrophy and become spindle shaped (Fig. 1). The characteristic appearance is a fragmentation and destruction of the metatarsal and the tarsal bones. The joint spaces disappear as

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consist of careful questioning of the patient for pain in the legs, especially in the calf muscles. Even when a negative reply is given, the calf should be tested for tenderness, and an attempt made to elicit Homans's sign. Whether or not the legs were examined postoperatively in 48 surgical cases, and if so, the findings are listed in Table 7. The case records contained no mention of postoperative examination of the legs in 25 patients. Of the 23 patients who were examined, the evidence of peripheral-vein thrombosis was positive in 5 and

the 4 fatal cases in 1945, only 1 of which can strictly be classified as nonpreventable. This case was that of a seventy-six-year-old woman in whom a supra-orbital neurectomy had been performed for right supraorbital neuralgia. Eight hours later she became cyanotic, the respirations were irregular, and she died within an hour. There was no warning of this embolism.

The first of the other 3 fatal cases in 1945 occurred in the patient described above as the second patient in Group 2. He had had repeated venous thromboses

TABLE 8 Composite Data in Entire Series of 52 Cases

GROUP	NO. OF CASES	CASES WITH HISTORY OF VENOUS TROUBLE	POSTOPERATIVE EXAMINATION OF LEGS			WARNING SIGNS BEFORE FATAL EMBOLISM
			NO MENTION	POSITIVE FINDINGS	NEGATIVE FINDINGS	
1 (death in 1 hour)	22	5	14	0	8	16
2 (death in 2-24 hours)	20*	4	6	3	9	18
3 (death over 24 hours)	10†	2	5	2	1	10
Totals	52	11	25	5	18	44

*One of these cases was medical.

†One of these cases was medical; another occurred in a patient who died before operation.

negative in 18. It is probable that in some of the 25 cases in which no mention of examination of the legs was made, signs of phlebothrombosis of the leg veins might have been demonstrated.

A composite picture of the entire series of 52 fatal cases is presented in Table 8. In these cases no measure to prevent pulmonary embolism was deemed justifiable in 1 patient with inoperable carcinoma. The most noteworthy and indeed surprising fact demonstrated, however, is that 44 of 52 patients gave warning of thrombotic processes. This means that in 85 per cent of the cases death from pulmonary embolism might have been prevented if the warning signs had been appreciated and prophylactic measures undertaken. Even 73 per cent of those patients who died of pulmonary embolism within an hour had given some warning signs, such as fever and tachycardia, several days before the fatal embolism. Since early 1942 anticoagulant therapy has been the treatment of choice at the Clinic for phlebothrombosis, with or without benign pulmonary embolism, and for thrombophlebitis, because of this there has developed a stimulus to be wary of thrombotic emergencies, and it is gratifying to note the drop in mortality that has occurred. In Figure 2 the mortality per year is tabulated in the 52 cases studied from 1940 to 1946. Little change is apparent in the first two years (1942 and 1943). The small number of deaths in 1944 and 1945 reflect the clinician's trend to become more conscious of thrombosis and embolism. It may now be possible to achieve a deathless year in cases of pulmonary embolism. That this objective may be closely approached seems possible on a review of

in the leg and a benign pulmonary embolism before femoral ligation was decided on. While being prepared for the procedure he died.

The third death in 1945 occurred in a fifty-two-year-old man in whom a Miles resection had been performed for carcinoma of the rectum. On the morning of the second postoperative day he became disoriented, and ten hours later lapsed into coma with convulsions and dilatation of the right pupil. Pulmonary embolism was entirely unsuspected, and no antithrombotic measures had been undertaken. Autopsy revealed a large embolism in the main pulmonary arteries and tiny thrombotic fragments in the pelvic veins, probably attributable to the operative site.

The fourth fatal case in 1945 was that of a fifty-three-year-old man on whom a Miles abdomino-perineal resection had been performed for carcinoma of the rectum. Wound evisceration occurred on the fourth postoperative day. The day after repair he went into shock and became cyanotic and dyspneic. He was treated for shock, peritonitis and atelectasis (by bronchoscopy). Two days later he died. No mention was made of examination of the legs postoperatively. The diagnosis of pulmonary embolism was apparently not entertained. Autopsy revealed atelectasis and peritonitis, but the direct cause of death was pulmonary embolism, thrombosis of the left common iliac vein was also observed.

SUMMARY

In a review of 52 fatal cases of postoperative pulmonary embolism the greatest number occurred in patients fifty to sixty years of age. Fifty-four per

ge was fifty-six years at the time the foot lesion was discovered The youngest patient was thirty and he oldest sixty-nine years of age The diabetes had

serologic findings were negative There was no clinical evidence of syphilis in any case. Evidence of neuritis was found in 14 of the 17

TABLE 1 Data in 17 Cases of Neuropathic Foot Lesions among Diabetic Patients (Continued)

CASE No	SEX	AGE	DURATION OF DIABETES	BLOOD HINTON REACTION	SPINAL-FLUID WASSERMANN REACTION	SPINAL-FLUID TOTAL PROTEIN mg /100 cc	EVIDENCE OF DIABETIC NEUROPATHY	ROENTGENOLOGIC FINDINGS	OTHER COMPLICATIONS	FOOT INVOLVED
10	M	43	11	Negative	Negative	35	Decreased sensation to pin prick and temperature changes and decreased vibratory sense in right foot	Proliferation and destruction of astragalus	Hypertension (mild)	Right
11	F	52	13	Positive	Negative	85	None	Destruction and proliferation of 3 cuneiform bones, proximal ends of 1st 4 metatarsals narrow irregular joint spaces	Hypertension (bilateral) and retinitis proliferans	Right
12	M	69	6	Negative	Negative	100	Anesthetic foot	Dense periosteal thickening of 4 lateral metatarsals narrow tarsal joint spaces with eburnation of joint margins	Hypertension	Right
13	F	55	14	Negative	Negative	57	Absent knee reflexes	Marked loss of cartilage between metatarsotarsal and intertarsal articulations irregular erosions of tarsal bones.	Hypertension albuminuria and diabetic diarrhea	Right
14	F	61	8	Negative	Negative	42	Mild painful neuritis and loss of vibratory and pinprick sensation	Both feet irregularity and destruction of proximal ends of all metatarsals and adjacent tarsal bones	Hypertension and diabetic retinitis	Right and left
15	F	69	7	Negative	Negative	66	Absent ankle reflexes and slight knee reflexes	Destructive process involving tarsals and proximal ends of all metatarsal bones, tarsal bone margins dense	Hypertension and diabetic retinitis	Right
16	F	45	18	Negative	—	—	Pupils irregular, no reaction to light in right pupil	Destruction and condensation of distal end of 1st metatarsal bases of all phalanges eroded internal cuneiform and scaphoid roughened and dense areas of absorption in proximal ends of 2nd and 3rd metatarsals	Hypertension	Right
17	F	62	5	Negative	Negative	59	Loss of sensation to pin prick in terminal 10 cm of left foot	Right destruction of 1st 2nd and 3rd metatarsals and first 4 toes Left similar changes in 1st metatarsal and first 4 toes Both complete disorganization of metatarsophalangeal joints	Hypertension diabetic diarrhea and albuminuria	Right and left

been present for an average of eleven and a half years
An examination of the spinal fluid was performed in 15 cases The Wassermann reaction was negative in all 12 cases in which the test was done Colloidal gold tests were negative in 8 cases and showed a moderate elevation to the left in 2 The spinal-fluid protein was elevated in 11 of the 14 samples, averaging 69 mg per 100 cc, with values of 100 mg in 2 cases
The blood Hinton test, which was negative in 15 cases, was positive, in 2, in which the spinal-fluid

cases Absent knee jerks, foot drop, anesthetic feet, loss of sensation to pinprick and vibration, bladder paralysis and paresthesias of the lower extremities, especially a feeling of numbness, were the most frequent manifestations individually and in combination Only 4 patients complained of the nocturnal pain in the extremities that often accompanies diabetic neuritis
Hypertension was present in 15 of the 17 cases, and the systolic pressure exceeded 200 in 7 cases A significant albuminuria (levels of over 100 mg per 100 cc) was recorded in 6 cases Two patients

their cartilage is lost, with a loss of continuity of the individual bones. Spontaneous fractures of the metatarsal bones may occur, spur formation and destructive and proliferative. In Case 1 autopsy disclosed mild degenerative changes of all joint elements, characterized by small islets of bone destruc-

TABLE 1 Data in 17 Cases of Neuropathic Foot Lesions among Diabetic Patients

CASE No	SEX	AGE	DURATION OF DIABETES	BLOOD HINTON REACTION	SPIRAL-FLUID WASSER-MANN REACTION	SPIRAL-FLUID TOTAL PROTEIN mg / 100 cc	EVIDENCE OF DIABETIC NEUROPATHY	ROENTGENOLOGIC FINDINGS	OTHER COMPLICATIONS	FOOT INVOLVED
1	F	29	20	Negative	Negative	19	Absent knee and ankle reflexes	Partial absorption, head of second metatarsal, first metatarsal irregular and dense	Hypertension, albuminuria and retinitis proliferans	Left
2	F	67	19	Negative	—	—	Bladder paralysis and absent knee reflexes	Destruction and partial absorption of tarsal bones and metatarsophalangeal joints bilaterally	Slight hypertension, albuminuria and diabetic retinitis	Right and left
3	F	63	15	Negative	—	33	None	Destruction of first cuneiform and scaphoid bones, destruction and pathologic fracture of proximal end of third metatarsal	Hypertension	Right
4	M	63	11	Negative	—	67	Absent knee and ankle reflexes	Destruction of joint spaces between tarsal and metatarsal bones, increased density of tarsal bones and of second metatarsal bone.	Slight hypertension and cataract	Left
5	F	56	14	Negative	Negative	100	Left peroneal paralysis, bilateral absent ankle reflexes and decreased sensation to pin point	Right: destruction of forward part of astragalus, most of the other tarsal bones and proximal ends of metatarsals. Left: similar less pronounced changes	Retinitis proliferans, albuminuria and coronary thrombosis	Right and left
6	M	59	11	Negative	Negative	60	Painful neuritis, anesthetic foot and loss of vibratory sense and sensation to heat and cold	Fragmentation and dissolution of continuity of the tarsal and proximal ends of metatarsal bones	Hypertension, albuminuria and diabetic retinitis	Right
7	M	30	7	Negative	Negative	61	Painful neuritis, paresthesias of feet, absent knee and ankle jerks and loss of vibratory sense in the feet	Half of scaphoid bone destroyed	Diabetic retinitis, hypertension and albuminuria	Right
8	M	63	14	Negative	—	59	Painful neuritis in arms and legs nine years previously	Proximal ends of 2nd and 3rd metatarsals and cuneiforms partially destroyed, anterior margin in cuneiform and scaphoid rough, irregular and dense	Retinitis proliferans, cataracts (bilateral) and hypertension	Right
9	F	61	2	Positive	Negative	—	None	Anterior tarsal bones dense and their outlines lost, proximal ends of metatarsals irregular and eroded	—	Left

ipping at the bone margins, characteristic of hypertrophic arthritis, are not seen.

Dr. Shields Warren examined histologically the foot lesions in Cases 1 and 6. In the latter a thigh amputation was necessary because of secondary infection. There was a complete loss of bone structure, numerous spicules of bone scattered throughout the area of involvement undergoing various stages of absorption and the remaining periosteum attempting to form new bone. These changes were partly obscured by the secondary infection. Thus, the lesion was like that in a Charcot joint, being both

tion with an increase in the number of osteoblasts. There were foci of mild degenerative changes of the synovial structure, with numerous areas of round-cell infiltration. Increased vascularity was observed in the pericapsular tissue, the walls of the larger vessels showing some thickening. Examination of several sections of the peripheral nerves revealed no definite abnormality.

CLINICAL AND LABORATORY DATA

Table 1 presents the pertinent data in these cases. In this series of 6 men and 11 women the average

In Key's series of 61 White and 9 Negro patients with Charcot joints, there were no cases in which the diagnosis of neurosyphilis could not be made from the physical and laboratory examinations. In approximately a third of the cases there were no premonitory symptoms, but in the remainder, various symptoms were present, including shooting pain, ataxia, bladder dysfunction, visceral crises, optical atrophy, disturbances of sensation in the lower extremities, Argyll-Robertson pupil, loss of deep reflexes in the lower extremities and a positive Romberg test. In 60 cases the blood Wassermann test was positive in 19 and negative in 41. In 30 cases the spinal-fluid Wassermann test was positive in 11 and negative in 19. Roentgenograms showed excess fluid in the joints and tissues, erosion of the weight-bearing surfaces, the production of new bone, pathologic fractures, loose bodies in the joints and, most important of all, diffuse sclerosis.

The most striking differences between the true Charcot joint and diabetic neuropathic feet are the acute onset of fluid in the joint and the swelling of the extremity that may occur in the Charcot joint, the presence of pain in the Charcot joint during the acute stage, the frequent occurrence of new bone formation in the Charcot joint and the rarity of bone formation in diabetic neuropathic feet, the syphilitic sclerosis of the bone in areas near the involved joint, the almost constant occurrence of other symptoms, signs and laboratory evidence of syphilis in patients with Charcot joints, and the relative infrequency of Charcot joints in the feet.

In this group of cases of diabetic neuropathic feet, there was no clinical evidence of syphilis, and the 2 patients with positive blood Wassermann reactions had negative spinal-fluid findings.

The possibility of ischemic changes secondary to arteriosclerosis was considered, but in 14 of the 17 cases the pulsations in the dorsalis pedis arteries were easily felt and there was no evidence of im-

paired circulation. In the remaining cases, the collateral circulation was poor in 1 and good in 2. These findings, as well as the rarity of the condition as compared with the marked frequency of extreme peripheral arteriosclerosis in diabetes of long duration, make the possibility that ischemic changes play an etiologic role extremely remote.

The findings of other evidences of diabetic neuropathy in 14 of the 17 cases, the fact that other nerve lesions produce similar bone changes and the trophic nature of the lesion all suggest that the arthropathy is a manifestation of diabetic neuropathy.

PROGNOSIS

None of the 17 cases showed any tendency to improve, and in most destruction gradually progressed. No treatment proved efficacious, but orthopedic appliances were used in an effort to relieve weight bearing and to avoid further deformity.

SUMMARY

Seventeen cases of neuropathic foot lesions are reported. All had destruction of the tarsal or metatarsal bones that was roentgenologically similar to that observed in Charcot joints.

Evidence is presented that this bone lesion is trophic in origin and is a manifestation of diabetic neuropathy.

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REFERENCES

1. Weinberg E. D. Treatment of Charcot joints. *South M J* 23:527-531 1930
2. Jordan W. R. Neurotic manifestations in diabetes mellitus. *Arch Int Med* 57:307-366 1936
3. Root, H. F. Medical aspects of diabetic surgery. *New York State J Med* 42:2296-2302 1942
4. Bailey C. C., and Root H. F. Neuropathic joint lesions in diabetes mellitus. *J Clin Investigation* 21:649 1942
5. Jordan W. R. Effect of diabetes on nervous system. *South M J* 36:45-49 1943
6. Rundles R. W. Diabetic neuropathy. *Medicine* 24:111-160 1945
7. deTakats G. Peripheral neurovascular lesion in diabetes. *Proc Am Diabetes A* 5:183 1945
8. Key, J. A. Clinical observations on tabetic arthropathies (Charcot joints). *Am J Syph* 16:429-446 1932

had diabetic nocturnal diarrhea, which is considered a manifestation of diabetic neuropathy

The eyes revealed diabetic retinitis in 9 of 15 cases, in 4 of which retinitis proliferans was distinguished by the ophthalmologist. The following is a typical case report

CASE 6 W W (Case 10917) developed diabetes in 1931, when he was 48 years old. He was first seen in March, 1932, with a history of ascites on and off for 5 years. Peritoneal catheter drainage had been instituted at another hospital. The tube was removed, and closure of the abdominal wound followed in 3 months without subsequent recurrence, no acid-fast bacilli were demonstrated. The patient was given 5 units of regular insulin daily and a diet containing 155 gm of carbohydrate, 71 gm of protein and 97 gm of fat (1777 calories)

He was not seen again until March, 1936, when the blood sugar was 520 mg per 100 cc, and he confessed that he had been careless with his diet. He had developed moderately severe neuritis in the legs and back, with absence of knee and ankle reflexes. The blood pressure was 140/80. The pulsations in the dorsalis pedis arteries were normal. There was no demonstrable leg weakness. The pains and paresthesias in the legs and feet, which were much worse at night, gradually subsided after treatment of the diabetes for several months and with supplementary vitamins. Routine x-ray examination of the left foot disclosed a fragmentation and dissolution of continuity of the tarsal and proximal ends of the metatarsal bones. The foot was thickened grossly, and there was flattening of the longitudinal arch. A diagnosis of neurotrophic foot was made.

In November, 1937, osteomyelitis of the left ankle and a spreading infection required a guillotine amputation followed in 1 month by a left thigh amputation from which the patient made an uneventful recovery. Histologic examination revealed a loss of bone structure and of continuity of the tarsal bones, spicules of bones undergoing absorption and the remaining periosteum attempting to lay down new bone. The joint spaces were lost.

On this hospital admission intermittent nocturnal diarrhea, often with nocturnal fecal incontinence, was first noticed. Examination of the urine revealed a slight trace of albumin, and the blood sugar was 450 mg per 100 cc on admission. The serum protein was 6.6 gm per 100 cc, with a reversal of the albumin-globulin ratio (0.74). The blood pressure was 150/90.

A year later the patient was again hospitalized with an infected callus on the right foot. A fluctuating blood pressure reached 192/110. There was a loss of vibratory sense in the lower half of the right leg and foot and a loss of sensation for hot or cold. The spinal-fluid Wassermann reaction, colloidal gold test and cell count were normal. On repeated examination 10 days later the total protein was 112 mg per 100 cc. He was discharged on December 18, the foot having healed. The nocturnal diarrhea persisted intermittently.

In March, 1939, the patient was readmitted with infection of the bone of the 4th and 5th right toes that required incision and drainage. At that time the neuritis had become much worse and the nocturnal diarrhea had persisted. He stated that the diabetes had been under poor control while 20 units of protamine zinc insulin were being taken. Knee and ankle reflexes remained absent. The infection responded after incision and drainage of the foot, which was done without anesthesia since he had loss of pain sensation in the foot—a so-called "anesthetic foot." He made a gradual recovery.

In January, 1941, the patient was readmitted to the hospital having received a burn on the side of the foot from a heater—the anesthesia had prevented his realizing the excessive heat. He recovered with conservative treatment. Examination of the urine revealed a quantitative albumin of 0.8 gm per 100 cc. On admission the blood sugar was 330 mg per 100 cc. On discharge the patient was advised to take 36 units of protamine zinc insulin daily.

He was readmitted in November, 1941, complaining of edema of the ankle of several months' duration, dyspnea on slight exertion and orthopnea. The blood pressure was 180/106. Cardiac enlargement with an apical systolic murmur was found, and there was a small bilateral pleural effusion. The urinary sediment contained many white cells, and a

phenolsulfonephthalein test showed 19 per cent excretion of the dye in 2 hours. The congestive failure responded to rest and digitalis therapy, and he was discharged in fairly good condition on November 29, only to be readmitted 16 days later with nausea and vomiting, slight mental confusion and dizziness. Spinal-fluid examination revealed a total protein of 60 mg per 100 cc but was otherwise negative. The blood nonprotein nitrogen was 51 mg per 100 cc, and the urinary sediment showed 20 to 30 white cells per high power field. The total protein was 5.5 gm per 100 cc. He improved and was discharged on January 3, 1942, although the ankle edema continued.

The final admission occurred only 3 days after discharge, when the patient again complained of nausea and vomiting, drowsiness and headache. The urine contained innumerable white cells, and there was a large trace of albumin. Examination of the blood disclosed a red-cell count of 3,800,000, with a hemoglobin of 12.2 gm per 100 cc, and a white-cell count of 10,400. An electrocardiogram revealed low T waves and small QRS complexes, suggesting myocardial damage.

The patient improved strikingly and was ready for discharge on February 5, when he suddenly developed marked dyspnea and cyanosis and collapsed. He died within 10 minutes.

Autopsy revealed a terminal massive pulmonary infarction. The right foot showed histologic changes similar to those previously found in the left foot but without evidence of infection. A partial loss of bone structure, with evidence of bone absorption was seen, with a loss of joint spaces.

DIFFERENTIAL DIAGNOSIS

It is believed that the bone destruction in these cases represents a trophic change resulting from diabetic neuropathy and is similar to the arthropathies that may result from neurosyphilis, syngomelia, nerve injuries and the neural form of leprosy. Since the neuropathic foot is painless, the patient continues to walk and hence to traumatize the softened bones, a deformed thickened foot resulting.

In view of the resemblance to the true Charcot joint of syphilis it is essential to distinguish the diabetic neuropathic foot from this condition. The differentiation is not always possible by x-ray examination alone.

The classic arthropathy of Charcot often begins as a sudden spontaneous swelling of the joint and is rarely preceded by injury or by pain. In the ninety-two joints in 70 patients reported by Key,⁸ injury had preceded the joint lesion in only 3 cases. The enlargement is due not only to an accumulation of fluid within the joint but also to periarticular swelling, which at times extends from the ankle to the knee. As the swelling increases, a feeling of tension and a variable amount of dull, aching pain in the joints may keep the patient awake at night. This acute stage may last for a week but subsequently subsides, with disappearance of the pain, and is succeeded by the chronic stage, in which the swelling is confined to the region of the joints and the disintegration of the joint progresses so that function is more or less impaired. Destruction and disintegration of the capsule and ligaments of the joint result in abnormal mobility. The articular cartilage is eroded, and the underlying bone may be eroded, with consequent fractures. Proliferation of cartilage and bone may occur, and there is often much thickening of the synovial membrane.

tube in place four and five days, respectively. There was no noticeable tissue reaction to the tube.

Poppe and de Oliveira⁶⁰ report that Polythene cellophane produced a marked fibrous reaction when wrapped around the aorta in experimental animals. This film caused more reaction than a commercial cellophane, which in the experiments caused little reaction. These workers used Polythene film to wrap around a syphilitic aneurysm to cause thicken-

Preliminary studies carried out to determine whether polyethylene had any inactivating effect on penicillin showed no significant diminution in the effectiveness of the drug after contact with sections of the tubing for twenty-four hours. Narat and Cipolla⁶¹ and Huelsebusch et al.⁶² reported a drastic reduction in penicillin activity after contact with certain plasticized forms of synthetic tubing, including Tygon and White Surgical Koroseal.

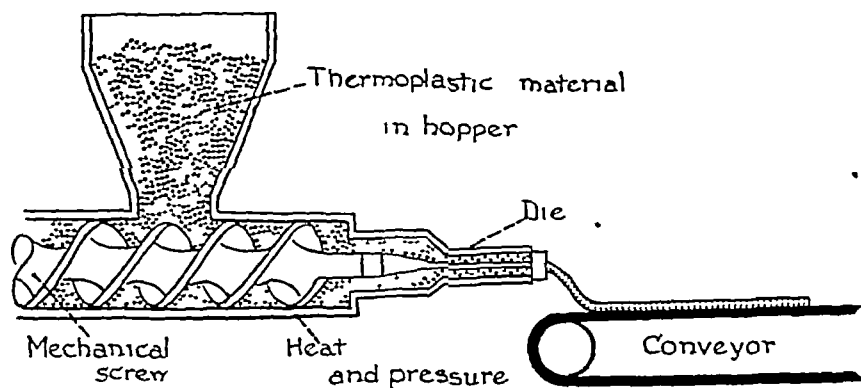


FIGURE 1

ing of the wall and obliteration of the aneurysmal sac. The use of the same material in aneurysms in 3 other cases and in a recurrent patent ductus arteriosus was mentioned, but none of the cases had been followed for a sufficiently long period to justify any conclusions. The experimental results of these workers are somewhat contrary to those of others reviewed below, particularly on the response to cellophane. They refer to Polythene cellophane or film, which in all likelihood was not pure polyethylene.

Ingraham, Alexander and Matson⁶¹ performed animal experiments to determine the reaction of cerebral tissue to polyethylene. Sections of pure polyethylene tubing of small diameter were buried in the cerebral cortex of cats, dogs, monkeys and rabbits. The animals were sacrificed at intervals of two to ninety days, and the cortex containing the polyethylene was submitted for histologic study. The amount of reaction to this plastic was slight, and the tubing was surrounded only by a thin fibrous tissue layer. Emphasis was placed on the importance of obtaining absolutely pure polyethylene for surgical use. A variety of products supplied to industrial concerns under the name of polyethylene and Polythene contain chemicals other than the pure polymer. These are in general irritating to human tissue and should not be employed. In brief, these studies indicate that pure polyethylene is well tolerated by the body, with a reaction similar to that following the use of methyl methacrylate.

None of the materials tested had any effect on streptomycin.

CELLULOSE PLASTICS

Cellophane

The cellulose plastics were among the first used in industry. In 1869 Hyatt laid the foundation for the modern plastics industry by mixing cellulose nitrate with camphor to form a plastic material. This product is at present called "celluloid" or "Pyralin." Many chemical modifications of this substance were subsequently developed to form other plastic materials with desirable qualities. Cellulose acetate, a compound that is less inflammable, more durable and more easily molded than cellulose nitrate, is an example. Plasticizers are necessary to make these materials pliable, tough and durable.

One of the most important cellulose plastics is that known as regenerated cellulose, commercially called "cellophane." The chemical composition of the finished product is similar to that of the original cellulose from which it is derived. A complicated series of chemical reactions is necessary to produce this product, but in general the cellulose obtained from cotton or wood reacts with caustic soda and carbon disulfide to form cellulose xanthate, which on immersion in an acid bath is converted into regenerated cellulose. For many of the commercial uses of cellophane, impermeability to water is desirable. This is made possible by surfacing it with

MEDICAL PROGRESS

SYNTHETIC PLASTIC MATERIALS IN SURGERY (Concluded)*

FRANC D INGRAHAM, M D,† EBEN ALEXANDER, JR, M D,‡ AND DONALD D MATSON, M D‡

BOSTON

✓ POLYETHYLENE

It has been known for many years that ethylene could be polymerized, but until 1936, when a new process involving high pressures was devised in England, only liquid and semiliquid polymers were obtained. Polyethylene was first employed experimentally in the United States in 1941.⁵⁷ The commercial use of polyethylene began here in 1943, when it was first produced in quantity.¹

Ethylene has a simple chemical structure, and polyethylene, which is a polymer of ethylene, is—theoretically, at least—the simplest structure in which a chain polymer can exist. It consists of carbon atoms joined in a chain, each one carrying two atoms of hydrogen. These chains, according to Bailey,⁵⁸ range in length from 200 to 1000 or more units.

Polyethylene (also called "Polythene") is a tough thermoplastic resin that has a slightly cloudy appearance. It is flexible, resistant to water and most other solvents and chemically inert. It maintains its toughness over a wide range of temperatures. None of its characteristics change within the extent of human body temperatures. It is tasteless and odorless. It is light, with a specific gravity of 0.92–0.95. By a method known to the plastics industry as extrusion, the material can be formed into rods, tubes, sheets or films. In the process of extrusion polyethylene is supplied in bulk form to a cylinder. Under pressure and heat within the cylinder, the final product is extruded through an aperture in the desired form (Fig 1).

One of the most desirable qualities of pure polyethylene from the point of view of use in the body is its flexibility without the addition of a plasticizer. On theoretical grounds because of its chemical inertness, simple chemical structure, resistance to water and pure state, this material should be well tolerated by tissues.

Polyethylene has found little place in medicine and surgery to date, but its flexibility, transparency and toughness and the facility with which it can be made into any size of tube or any thickness of film suggest multiple uses in the field of surgery.

Several possible drawbacks to the surgical applications of polyethylene should be mentioned. Since it is widely employed in industry because of its electric-insulating characteristics, manufacturers sometimes further enhance these properties by the addition of other chemical substances, known as antioxidants. Because one rarely knows what the added substances are, they must be considered harmful to the body unless proved otherwise. In obtaining this material, *pure* polyethylene should be specified. Manufacturers also state that polyethylene is occasionally extruded through a machine that has previously been used to extrude another substance containing a plasticizer or another chemical compound. It is apparently difficult to free the extruding apparatus completely of these substances, and for commercial use this is rarely necessary. Consequently, if this material is to be employed in surgical procedures, it is advisable to test small portions in experimental animals to be certain that it does not contain added chemicals irritating to the body. The material might, if found useful in a variety of surgical procedures, be dispensed by commercial medical-supply houses, which could take the responsibility of supplying a pure product.¶

Polyethylene will not tolerate sterilization by autoclaving, but it can be sterilized by boiling. It tends to retain the curve or shape in which it is placed during the process of boiling. Chemical sterilization by immersion in a 1:1000 solution of Zephiran for eighteen hours has been found satisfactory provided care is taken to see that the solution reaches the lumen of the tube and that the plastic, which is lighter than water, is kept completely in the solution and not floating on the surface.

Meyers⁵⁹ described a procedure of inserting a piece of small-caliber polyethylene (Med-O-Seal) tubing into a vein through a needle. This has provided a satisfactory method of giving repeated or constant intravenous injection through the same tube over prolonged periods without immobilizing the arm or leg. If intermittent injections are required, the tube is filled with physiologic saline solution at the completion of each injection, and the open end is plugged. Clotting does not take place within the tubing by this method, which Meyers used in 9 cases, in 2 of which he left the intravenous

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¶Polyethylene is now furnished by A C Balfour Associates, Englewood, New Jersey as "Med-O-Seal."

ense reaction occurred consisting in a collection of gelatinous or purulent fluid around which the fibrous tissue contained phagocytic mononuclear cells. A dense scar-tissue band was formed around the arteries wrapped with cellophane.

Gross,⁷⁴ in several of his early cases, wrapped the Pont P T 300 cellophane around the patent ductus arteriosus after it had been ligated. He found that the material aided in maintaining occlusion of the patent ductus arteriosus. More recently, he has found its use unnecessary, since he has been able successfully to divide and suture the ductus in the majority of the cases. The use of cellophane for this purpose has also been reported by Harper and Robinson,⁷⁵ and Harrison and Chandy⁷⁶ have employed it to occlude a subclavian aneurysm.

One can only conclude that cellophane is a strong tissue irritant and a potent stimulator of scar formation. There may be, and probably are, certain types of cellophane that are less irritating than others, but all experimental and clinical work that has been accompanied by adequate histologic studies confirms the conclusion that the material is irritating in the body. Its use, therefore, should be limited to the laboratory or to clinical cases in which a localized layer of scar tissue is desirable for therapeutic reasons.

Celluloid

Closely allied to cellophane chemically is another cellulose derivative, cellulose nitrate, mentioned above. This is better known by its trade name of "celluloid." As a general rule, camphor is used as a plasticizer for cellulose nitrate to produce the finished product.

For twenty years after World War I, sporadic reports of the use of celluloid as a material to fill skull defects appeared. An adequate review of this subject has been made by Grant and Norcross,⁷⁷ who found the material unsatisfactory in their own small series. In 1 case the celluloid plate was removed because of postoperative headaches. It was found to be enclosed in a sac formed by the pericranium and adherent to both pericranium and dura. The authors stated that the membrane was "several millimeters thick and was intimately connected with the dura, from which it was peeled off in layers until healthy dura was reached."

Ney⁷⁸ reported the use of celluloid in cranioplasty in 300 cases, with satisfactory results. He stated that there were infections in only 5 cases, although in all cases drains were left in the wounds for forty-eight hours and in most cases fluid continued to form over the plates for days or weeks. There were no histologic studies in this series, and there was no mention of a long-term follow-up study in any large percentage of the cases.

Woolf and Walker¹¹ reviewed the subject of cranioplasty and concluded that celluloid causes a moderate tissue reaction but that many such plates have

remained in place for long periods. They stated that the material became brittle and friable after prolonged periods in the body. In view of the more recently developed alloplastic grafts that have proved easier to handle and are better tolerated by the body than celluloid, there seems little need for its use in cranioplasty.

MISCELLANEOUS PLASTICS

In addition to the plastics described above as attaining relatively wide fields of usefulness in surgery, isolated reports of studies with other materials are found in the literature. In general, such reports illustrate the clinical use of plastics that seem to have desirable physical properties, without well controlled experimental or follow-up studies. Smith-Petersen⁷⁹ used a bakelite mold as a hip cup in an arthroplasty. The patient was reported as benefited when last seen two years after the operation. Bakelite is one of the organic synthetic resins of the phenol-formaldehyde group, so far as can be determined, no study of the response of tissue to such compounds has been made.

Baker⁸⁰ reported a new type of plastic hip cup for arthroplasty but did not mention the type of plastic used. He was primarily concerned with the form that the cup should assume in relation to the head of the femur.

Bellas⁸¹ described histologic studies of a suture material called "Plastigut," which he described as a polymerized condensation product of aliphatic and aromatic alcohols with short-chain aliphatic aldehydes. The material was further described as a nonreacting, nonabsorbable, noncapillary suture that was satisfactory in surgical procedures. The histologic sections displayed showed little tissue reaction to the Plastigut.

Blaine⁸² made various plastic materials out of casein, fibrin and other protein products. These plastics were formalized for varying periods. They were buried in the long bones of rabbits and studied at intervals. The protein plastics were all completely absorbed, the rate of absorption being inversely proportional to the degree of formalization. They maintained strength for only three or four weeks. Blaine noted that the breakdown of the proteins was probably "responsible for the heavy cellular infiltration commonly noted at an intermediate stage at the margin of the softened plastic." Nevertheless, he considered these plastics well tolerated. He did not believe that such products as he used were suitable for use in human subjects.

To illustrate the difficulty occasionally encountered in carefully delineating the field of plastics, reference should be made to methyl cellulose, which is manufactured industrially as a mucilage and is soluble in cold water, giving a water-clear, viscous colloidal solution. It has been described as a methyl ester of cellulose and consists of a long chain of dextrose molecules. Hueper, Martin and Thompson⁸³

a thin film of cellulose nitrate lacquer. Cellophane is formed in thin transparent sheets that are used for many purposes, prominent among which is the wrapping of packages of cigarettes.

Cellophane, with its smooth surface, pliability, toughness and transparency, has attracted the attention of many surgeons. Its properties invite its use in the human body as a covering or sheath where the normal coverings are lost.

Perhaps nowhere in the medical literature are there sharper contradictions regarding the reaction of a given material in the body than in the articles on cellophane. Some authors have maintained that it causes little or no reaction, whereas others have found that it incites an intense tissue reaction. One of the inherent difficulties has been the negligence of some of those who have reported on the use of cellophane to specify exactly what type they used. There are several different products, some treated with other chemicals to make them impervious to water. Probably many workers who have used these products with conflicting results have employed dissimilar chemical materials.

Another difficulty arising from the use of cellophane in surgery is the inaccessibility of information regarding plastic products from the manufacturers themselves. Chemicals may be used to treat plastics that are considered trade secrets by the industrial concerns that produce them. In general, the reports that cellophane is well tolerated by the body have been based on a few clinical trials unsupported by experimental work or histologic studies of tissues. The more careful studies of cellophane have shown it to incite such a foreign-body response that this particular quality has been used in unusual circumstances when intense scarring is desired.

Wheeldon⁶³ used cellophane that he designated "No 300, moisture-proof, transparent film, 0.00088 inches thick." He performed a hip and a knee arthroplasty in which this material was employed as an interposition membrane, and the substance was also used in a tendon operation as a sheath. All the patients were reported to have benefited by the operations, and Wheeldon considered cellophane reactionless. No tissue-reaction studies were reported.

In like manner, McKeever⁶⁴ used No 300 cellophane in 4 cases as an interposition membrane in synovectomy, and considered it satisfactory. Harley and Breck⁶⁵ employed cellophane from cigarette packages in joint and tendon operations. They sterilized the material by boiling for twenty minutes and later "wiped off the waterproofing material." The patients were followed for only a few weeks and were reported as much improved by the operations.

Donati,⁶⁶ in Italy, used a commercial cellophane to replace the dura in a series of animal experiments. He reported that the brain showed no unusual reaction and that no adhesions were formed between the cerebral cortex and the material. The exact

type of cellophane employed was not recorded and there was no mention of its use in human patients.

In the Russian literature, Christyakov⁶⁷ recommended the utilization of cellophane as a protective covering over open or infected wounds. In the same communication, cellophane was reported to be satisfactory as a sheath around the anastomotic site in peripheral-nerve sutures. It had been used in 9 cases, as well as in 2 tendon operations. In the nerve anastomoses in 2 cases and in both the tendon cases, it was subsequently necessary to remove the cellophane, presumably because of infection.

In addition to the papers mentioned above, Poppe and de Oliveira⁶⁸ recently published an article describing experimental attempts at occlusion of vessels with various plastic materials. They reported the use of "No 300 P N T 71" and "No 300 P T 62" cellophanes, which, they stated, are cellulose hydrate, nonmoisture proof and insoluble in water and dilute acids. They were said to produce little reaction when wrapped around the aorta of an experimental animal. No other mention was made of the type of reaction and no photomicrographs were shown, but the efficacy of cellophane in producing scar around a major artery was less than that of other materials used, including Polythene film.

In sharp contrast to the reports of authors who consider cellophane well tolerated by the body is a series of papers, most of them the accounts of careful experimental, clinical and histologic studies, condemning the material as an irritating foreign body or recommending it for use in tissue because of its ability to stimulate the formation of scar tissue. Indeed, as a result of work reported by Page,^{68, 69} Graef and Page⁷⁰ and Dunhue,⁷¹ the term "cellophane perinephritis" has been coined. This describes a type of dense scar tissue that forms around a kidney after a piece of du Pont P T 300 cellophane has been wrapped around it. This is a reliable method of producing experimental hypertension in animals. It causes an intense inflammatory reaction, with the attraction of many polymorphonuclear leukocytes followed by continuous fibroblastic activity and deposit of collagen. The cellophane does not disappear, and the response lasts as long as there are cells and vascular channels around the cellophane to permit reaction. This type of reaction of tissue to the material has also been found by Bailey and Ford,⁶¹ who buried cellophane in the abdominal wall of guinea pigs and studied histologic sections of the tissue removed at various intervals.

Following the work of Page,^{68, 69} Pearse^{72, 73} studied the experimental occlusion of large arteries in animals by the use of du Pont P T 300 cellophane. In several animals complete closure of the aorta was obtained by this method. Pearse observed that this material was an extreme tissue irritant, since an in-

Adequate experimental trial should precede the clinical use of any untested plastic material in surgery

REFERENCES

57 Simonds, H. R. and Ellis C. *Handbook of Plastics* 1033 pp New York D Van Nostrand Company, Incorporated 1943

58 Bailey R. L. *Polythene Used in Britain as Insulator in British Aircraft 1941* E. I du Pont de Nemours and Company Incorporated

59 Meyers L. Intravenous catheterization *Am J Nursing* 45 930 1945

60 Poppe, J. K., and de Oliveira H. R. Treatment of syphilitic aneurysms by cellophane wrapping *J Thoracic Surg* 15 186-195 1946.

61 Ingraham F. D. Alexander E., Jr., and Matson D. D. Unpublished data.

62 Huelsbusch J. B., Foter M. J., and Gibby I. W. Effect of rubber tubing upon stability of penicillin and streptomycin solutions *Science* 104 479 1946

63 Wheelton T. Use of cellophane as permanent tendon sheath *J Bone & Joint Surg* 21 393-396 1939

64 McKeever, D. C. Use of cellophane as interposition membrane in synovectomy *J Bone & Joint Surg* 41 576-580, 1943

65 Harley G. H., and Breck L. W. Cellophane in bone and joint surgery *Am J Surg* 68 229 231 1945

66 Donati D. Ricerche sperimentali sull'uso del cellophane in plastica dorsali di varia grandezza *Bull d sc med Bologna* 109 425-432 1937

67 Chistyakov N. L. Use of cellophane in treatment of wounds *Am Rev Soviet Med* 3 490-493, 1946.

68. Page, I. H. Method for producing persistent hypertension by cellophane. *Science* 89 273 1939

69 *Idem*. Production of persistent arterial hypertension by cellophane perinephritis *J A M A* 113 2046-2048, 1939

70 Graef I. and Page I. H. Pathological anatomy of cellophane perinephritis *Am J Path* 16 211-222 1940

71 Dunbar F. W. Effect of cellophane perinephritis on granular cells of juxtaglomerular apparatus *Arch Path* 32 211-216 1914

72 Pearce H. E. Experimental studies on gradual occlusion of large arteries *Anr Surg* 112 923-937, 1940

73 *Idem*. Experimental studies on gradual occlusion of large arteries *Tr Am S A* 58 443-457 1940

74 Gross R. E. Complete surgical division of patent ductus arteriosus report of fourteen successful cases. *Surg, Gynec & Obs* 78.36-43 1944

75 Harper F. R., and Robinson M. E. Occlusion of infected patent ductus arteriosus with cellophane. *Am J Surg* 64 294-296, 1944

76 Harrison P. W. and Chandy J. Subclavian aneurysm cured by cellophane fibrosis *Anr Surg* 118 478-481 1943

77 Grant F. C. and Norcross N. C. Repair of cranial defects by cranio-plasty *Anr Surg* 110 488-512 1939

78 Nev K. W. Repair of cranial defects with celluloid *Am J Surg* 44 394-399 1939

79 Smith-Petersen M. N. Arthroplasty of hip new method *J Bone & Joint Surg* 21 269 288, 1939

80 Baker D. R. New type of plastic hip cup for arthroplasty or for use as artificial femoral head *Guthrie Clin Bull* 11 133 1942

81 Bellas, J. E. Suture studies new suture *Arch Surg* 41 1414-1425 1940

82 Blaine G. Experimental observations on use of absorbable and non-absorbable plastics in bone surgery *Brit J Surg* 33 245-250 1946

83 Hueper W. C. Martin G. J. and Thompson M. R. Methylcellulose solution as plasma substitute *Am J Surg* 56 629-635 1942

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT
TRACY B MALLORY, M.D., Editor
BENJAMIN CASTLEMAN, M.D., Associate Editor
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CASE 33111

PRESENTATION OF CASE

A thirty-seven-year-old Swedish asbestos worker entered the hospital because of cough and chest pain

Two and a half years before admission the patient had developed a cough, nasal congestion, nasal discharge, fever and shortness of breath that had persisted one week and had been followed by a dull, aching pleuritic pain along the left costal margin

He was hospitalized for a week and then rested at home for four months

In the hospital about 1000 cc of fluid was removed from the left side of the chest. Subsequently, he returned to work and felt well except for a morning cough productive of small amounts of odorless white sputum

Occasional chest pain and exertional dyspnea were also noted

A year and a half later there was an insidious onset of weakness and fatigability and a gradual loss of 25 pounds in weight

Three months before entry the pleuritic pains became persistent, and the weakness and dyspnea severe, and the patient slept propped on two pillows

Repeated sputum smears were negative for tubercle bacilli

The patient's work consisted in cutting asbestos insulating board, he denied exposure to undue

amounts of dust

There was no history of exposure to tuberculosis

Physical examination revealed the patient to be orthopneic and breathing rapidly at a rate of 30 per minute, with a dry, hacking cough and clubbed fingers

There was a slight, shotty, generalized lymphadenopathy

Respiratory expansion on the left was diminished, as were tactile and vocal fremitus and breath sounds

On the right there were increased bronchovesicular breath sounds and scattered dry rales

The heart and mediastinum were shifted to the right, and the apical beat was maximal in the right midclavicular line

There was a ticktack rhythm with a rate of 110, and a pulsus paradoxicus

The abdomen was normal

The temperature was 100°F

The blood pressure was 128 systolic, 70 diastolic

Examination of the blood disclosed a red-cell count of 4,900,000 and a white-cell count of 12,200, with 77 per cent neutrophils, 16 per cent lymphocytes and 7 per cent monocytes

The urine and stools were normal

X-ray examination showed numerous discrete areas of increased density scattered over the right lung, pressing on the lower trachea and left main bronchus and deviating them to the right was a large mass measuring 11 cm in diameter (Fig 1)

A small amount of aerated lung was seen at the periphery of the mass

There was either fluid or, more probably, dense pleural thickening and collapsed lung between the mass and the lateral costal margin

The left lower-lung field was almost completely opaque

In the hospital the patient's condition became steadily worse

Further x-ray studies showed displacement of the esophagus to the right (Fig 2), extensive periosteal new bone formation of the left upper ribs, slight displacement of the stomach to

recommended it for use as a plasma substitute in place of acacia. It was fairly well tolerated in animals when given as a 2 per cent solution intravenously, but it has the disadvantage of being stored in the liver, spleen and kidneys. Presumably, since the advent of readily available plasma during and following World War II, it will not be widely used in blood-replacement therapy.

DISCUSSION

A factual review of the application of industrial plastics in the field of surgery has been presented. The tremendous variation in plastic materials, with the production of literally thousands of different types, is at first sight confusing, but on closer study it is evident that for the selection of materials to be buried in human tissues, certain definite criteria are necessary. Primarily, such criteria forbid the use of any plastic that can do harm to the body either by toxicity or by irritating properties causing excessive scar-tissue formation. There are certain exceptions to this rule in the use of materials to cause the formation of a localized area of scar tissue, as in the obliteration of a patent ductus arteriosus or the surgical treatment of aneurysms, but the exceptions are few and well known.

Choosing industrial plastics for use in surgery is therefore much more than a selection of certain materials that possess desirable physical properties. In general, plasticizers incorporated within plastics are not well tolerated by the body. The exclusion of all plastics containing plasticizers greatly narrows the field of selection, when the field has been further delineated by the requirements imposed by necessary physical properties for specific uses, a small number of plastic materials remain. From the review presented above, it is all too obvious that frequent clinical use of plastics has been made without any controlled studies. Consequently, many publications on the employment of plastics in surgery are merely the reports of the isolated use of some plastic material in clinical surgery.

In an attempt to be exact in the study of plastics, a difficulty is encountered — namely, the possession of certain commercial secrets by industrial concerns. As a result, in experimental work with plastics it is sometimes impossible to obtain information regarding the chemical make-up of the compounds used. Furthermore, the industrial utilization of plastics does not require the same purity as the surgical use of the same materials. If an apparatus employed to produce a plastic tubing, for example, has been previously used to produce some other material, it may contain minute quantities of irritating chemicals of no significance to industry but of potential harm in surgical procedures. This factor must be taken into consideration, particularly when plastic tubing such as polyethylene is employed. The dispensing of a standard product of

nylon sutures by medical-supply houses minimizes the importance of this point for such material. Methyl methacrylate can be easily polymerized as a pure chemical product with little danger of added chemical impurities. Cellophane is in no sense of the word a pure product, and in view of the fact that it should be used only where localized scar tissue is desired, the problem resolves itself into a search by the investigator for commercial brands of the product that are sufficiently irritating to the body for the desired use.

There are many obvious discrepancies in the medical literature dealing with plastics — disagreements that do not appear reconcilable. In the main, these discrepancies are based on the failure of some investigators to specify exactly the plastic product used in the work they have reported. In some instances it has been difficult, because of commercial secrets, to obtain detailed information, and in others it appears that impurities, of which the investigator was unaware, were included in the materials. Whatever the reasoning behind the reporting of the surgical use of plastics without exact knowledge of the plastic, the practice of choosing such materials for clinical trial because of their desirable physical properties alone should be abandoned. Sufficient knowledge regarding plastics is now available to enable one to choose a material that is well tolerated as well as one that possesses desirable physical properties. If other materials are needed, or if promising new plastics appear, their clinical use should be preceded by adequate experimental study.

Three plastic materials have been found to be well tolerated by the body, and in aggregate they offer an imposing list of desirable physical properties from which a selection can be made for surgical use. Methyl methacrylate (Lucite, Plexiglas), a pure polymer that is hard, transparent, and easily cast into desired forms, can be used for cranioplasty, for implants in various parts of the body and in the form of rigid tubes. Nylon, in the form of a filament, is at present employed only as a suture material. Polyethylene (Polythene) is a polymer of simple chemical structure that is pliable, soft and relatively transparent. Its primary value has been in the form of tubing.

SUMMARY

A review of the medical literature regarding industrial plastics is presented. Three plastic materials are well tolerated by the body: methyl methacrylate (Lucite, Plexiglas), nylon sutures and polyethylene (Polythene).

Cellophane is in general a severe tissue irritant, of use in surgery only to incite scar tissue.

A variety of other plastic materials have received sporadic clinical trial but are not recommended.

the left lung or from a mediastinal tumor. I should like to ask Dr. Schatzki whether he has ever seen rounded shadows of this size and density that were not due to tumor.

DR. RICHARD SCHATZKI: Yes.

DR. KING: I stand corrected on that point.

DR. SCHATZKI: That does not mean that this was not a tumor.

DR. KING: I have never seen rounded shadows of this size and distribution with silicosis, tuberculosis

air left in the left lung is the small amount seen in the left upper lung. The films do not show what is going on lower down.

DR. KING: So you will not help regarding the position of the tumor—that is, whether it is in the lung or outside the lung?

DR. SCHATZKI: I think that I could help if I was allowed to.

DR. KING: I think that it would be all right, how about it, Dr. Castleman?



FIGURE 2. Roentgenogram of the Chest and Abdomen following a Barium Swallow Showing Displacement of the Esophagus and Stomach by a Mass in the Left Side of the Chest.

or in fact anything, and I therefore believe that the process in the right lung was definitely a metastatic tumor. The x-ray film of the left side of the chest shows a large, round mass displacing the trachea and the left main bronchus to the right. Is the tumor in the lung itself or in the mediastinum?

DR. SCHATZKI: The same mass is visible on this film in the same position. I do not believe that one should try to delineate the exact outline of the tumor when so little air is present. Other criteria should be used to demonstrate the mass. The only

DR. BENJAMIN CASTLEMAN: By all means.

DR. KING: I need a great deal of help.

DR. SCHATZKI: There is some definite evidence of a large mass outside the lung. The first indication is the position of the esophagus, which is displaced far to the right side by a mass. This mass has a diameter much larger than the mass in the upper-lung field, and therefore it cannot be a tumor in the lung. The second point is the position of the fundus of the stomach, which is pushed downward in contrast to what one would expect with a lung tumor.

the left, enlargement of the spleen and the suggestion of a retroperitoneal mass rotating the left kidney. Three attempted thoracenteses failed to encounter fluid, although the needle was inserted to a depth of 5 cm. No acid-fast organisms were found in the sputum. Tuberculin tests were negative in a 1:1000 dilution. The patient became ex-

the final hospital admission, with fever for a week. About 1000 cc of fluid was removed, following which the patient was discharged from the hospital. He then rested at home for four months, returned to work and remained in good condition for a year. This could have been pleurisy with effusion, perhaps tuberculous. Many sputum examinations, however,



FIGURE 1 Roentgenogram of the Chest, Showing Opacity on the Left and Multiple Nodules in the Right Lung

tremely weak and dyspneic and perspired constantly. He died on the thirty-seventh hospital day.

DIFFERENTIAL DIAGNOSIS

DR DONALD S. KING: This seems to be the old problem of a tumor in the lung with a decision to be made regarding the kind of tumor. As in most cases, the decision will be based largely on the x-ray appearance.

One should comment first on the occupation. This man worked with asbestos, cutting insulating board. Exposure to asbestos causes lung changes but never, in my experience, to the extent that was present in this case. I believe that asbestosis was not a factor in the illness and that, if present, it was of secondary importance.

The next question concerns tuberculosis. The onset of the disease was two and a half years before

showed no tubercle bacilli, and shortly before death a tuberculin skin test was negative in a 1:1000 dilution. In any event, the evidence for tuberculosis does not seem sufficient to justify that diagnosis in addition to what I believe was a tumor. My diagnosis is tumor, with fluid that was secondary to the tumor and not due to tuberculosis or other infection.

The x-ray films present a different picture on each side of the chest. On the right side there are many nodules, which are better shown in some films than others. In my experience, rounded nodular shadows of this sort have always been caused by metastatic tumor, either from some spot elsewhere in the lung or from some place outside the chest. If the tumor was metastatic from outside the lung, it could have been from above the clavicles or below the diaphragm, or there could have been metastases from a primary bronchiogenic cancer in

oses of x-ray therapy were given, without effect in the lesion. We were able to get a needle biopsy shortly before death. A mass developed above the left clavicle about 5 cm in diameter, and we thought that there was also a mass in the epigastrium.

DR KING: Such metastases would be against my diagnosis. A primary carcinoma of the lung would be likelier to metastasize to the neck, although lymphoma could do so.

CLINICAL DIAGNOSIS

Carcinoma of lung, probably metastatic

DR KING'S DIAGNOSIS

Mediastinal teratoma, with metastases to right lung

ANATOMICAL DIAGNOSIS

Mesothelioma of pleura and pericardium, with metastases to right lung and retroperitoneal lymph nodes

PATHOLOGICAL DISCUSSION

DR CASTLEMAN: The left lung was completely encased on all sides by a thick, hard, somewhat

from any parenchymatous tumor nodules. The heart and pericardium together weighed 1100 gm. The heart itself was perfectly normal, the increase in weight being due to the tremendous thickening of the visceral pericardium, which measured as

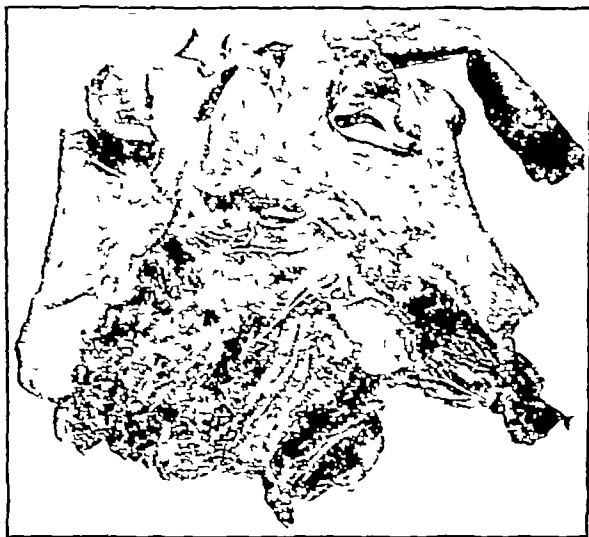


FIGURE 4 Photograph of the Heart Showing Neoplastic Involvement of the Visceral Pericardium

much as 3 or 4 cm in thickness (Fig 4). This gross picture of involvement of the pericardium and



FIGURE 3 Photograph of Coronal Section of the Left Lung, Showing Complete Encasement by the Pleural Tumor

shiny, fibrous tumor compressing the lung into a small fraction of its normal volume. In places this thickening of the pleura or tumor tissue involving the pleura measured as much as 8 cm (Fig 3). There were multiple tumor nodules in the right lung, but no involvement of the pleura. This was in sharp contrast to the left lung, which was free



FIGURE 5 Photomicrograph of the Mesothelioma

pleura fits in with the diagnosis of mesothelioma. We examined the bronchi carefully throughout the left lung and found no evidence of tumor within a

that has produced collapse. Thirdly, the ribs, if anything, are spaced farther apart than on the normal side, which is again unusual for a lung that has collapsed.

DR KING I should have committed myself before I asked that question, but I agree with your conclusions. I cannot be sure that this was not a bronchiogenic carcinoma of the left upper lobe, but my opinion is against that diagnosis. There was also involvement in the left lower lobe. I suppose that this also may have been a tumor. Do you want to commit yourself on that, Dr Schatzki?

DR SCHATZKI I think that I know the answer. It is obvious, as I have said, that there was something outside the lung, otherwise, the stomach would not have been displaced or the ribs separated.

DR KING Do you think that it was a tumor or fluid?

DR SCHATZKI I believe that it was a tumor.

DR KING That is what I believe.

Let us go down to the abdomen. Was the spleen enlarged or was it displaced downward? I should like to omit the spleen if I may.

DR SCHATZKI So far as I am concerned, it may be excluded.

DR KING Was the stomach involved?

DR SCHATZKI There is no evidence of involvement of the stomach. It was displaced, but this was due to the low position of the left leaf of the diaphragm.

DR KING Was the liver enlarged? And was the displacement of the stomach to the left due to such enlargement?

DR SCHATZKI The liver was not enlarged so far as I can tell.

DR KING This is an intravenous pyelogram showing a retroperitoneal mass rotating the left kidney.

DR SCHATZKI Both kidneys are low in position, and I am wondering if what we see is not again due to the low position of the diaphragm.

DR KING You do not see the retroperitoneal mass?

DR SCHATZKI Not that I can be sure of. I do not see the outline of the kidneys so well as I should like to. The upper pole of the right kidney is clearly seen, but the upper pole of the left kidney is not.

DR KING I suppose that you have helped all you can. Do you want to say anything more?

DR SCHATZKI Yes, there are some rib changes.

DR KING You mean the periosteal changes in the rib? I have seen such changes only with pus. Have you seen periosteal changes with large tumor masses?

DR SCHATZKI We have seen them in patients who did not have empyema but who had a chronic nonspecific process in the lung.

DR KING The films show the periosteal changes clearly, and I am inclined to agree.

Actually, we have no evidence of any source of

tumor outside the chest, but the possibility of tumors in the pharynx and the thyroid gland should be mentioned because findings similar to those in this case follow metastases from malignant tumors in those areas. We are not justified, however, in making such a diagnosis with the evidence at hand. Below the diaphragm there is no indication of disease of the stomach, pancreas, liver or kidney. These films at first suggested that the testicle or the prostate was the primary source, or perhaps a so-called "hypernephroma." This is a fairly characteristic picture for metastases from the testicle or prostate, but we have no evidence to make that diagnosis. There does not seem to me to be any justifiable source for the tumor outside the chest, and we are back to the problem of what this tumor was.

Was it bronchiogenic or mediastinal? We have seen exactly this picture with teratomas of the mediastinum that have eventually broken loose. If it was a lung tumor I lean toward a bronchiogenic carcinoma with metastases to the right lung and possibly the retroperitoneal area. The findings were not quite consistent with those of bronchiogenic carcinoma because such tumors are usually not large enough to push the mediastinum to the other side unless a great deal of fluid is present. Also, the rib changes were more like those with a large tumor mass that had been pressing on that area for some time. The process had been going on for perhaps two and a half years. My diagnosis is a mediastinal tumor, probably a teratoma, with metastases to the right lung. I do not believe that the tumor was a lymphoma, although again that must always be considered. I doubt whether it was a bronchiogenic carcinoma with metastases.

DR F DENNETTE ADAMS How do you exclude lymphoma?

DR KING I do not exclude it. I have not seen x-ray findings such as these with lymphoma, which usually causes more symptoms than this man had for two and a half years. The other conditions I have named seem likelier.

DR ALFRED KRANES Is it not unusual for fluid due to tumor to subside for so long a time?

DR KING Yes, that is one of the things against trying to explain the whole picture as tumor. I agree that subsidence of all symptoms for a year after the removal of 1000 cc of fluid in a case of tumor is not usual. I wanted to make the diagnosis of tuberculosis, but I could not.

DR CHARLES L SHORT I saw this patient on the ward, and I went through much the same line of reasoning as Dr King has. From the history my impression was tuberculosis, but from the x-ray findings that certainly could not have been the primary diagnosis. I do not believe that most of us went so far as Dr King in being willing to say that the tumor was primary in the chest. We thought of lymphoma and for that reason small

chloride content was 301 and the chloride 91 milliequiv per liter. The prothrombin time was 8 seconds (normal, 14 seconds).

The urine was acid, had a specific gravity of 1.026 and gave a +++ test for albumin. It did not contain sugar or diacetic acid. The sediment showed many hyaline and some granular casts, as well as 6 white cells per high-power field. X-ray films of the chest and stomach showed the diaphragm to be high in position, and there were segmented areas of atelectasis in the left lower lobe. The stomach was greatly distended by gas. The small intestine contained a moderate amount of gas but was only slightly dilated. The colon was not distended, but the right side contained a large amount of fecal material.

During the day the patient gradually became drowsy. She was given 1500 cc of 5 per cent dextrose in physiologic saline solution and 900 cc of 5 per cent dextrose in water, and administration of 100,000 units of penicillin every three hours was begun. In the afternoon the chloride had fallen to 74 milliequiv per liter. The patient was cold and clammy and appeared sicker, although the abdomen was softer and peristalsis was improved. The blood pressure was 160 systolic, 90 diastolic, and the pulse was strong. The cecostomy drainage was 475 cc. The urine output had fallen off, although the actual amount was not recorded.

On the third hospital day the patient seemed somewhat more alert. The abdomen was much softer, and peristalsis was fairly good. The heart sounds, however, were distant, with a ticktack rhythm. The hematocrit was 57. The protein was 8.5 gm, the nonprotein nitrogen 155 mg and the blood sugar 200 mg per 100 cc, the chloride was 85 and the carbon dioxide 30.8 milliequiv per liter. The patient was given 3000 cc of 5 per cent dextrose in saline solution and started on 8 units of insulin. The cecostomy drainage was 230 cc.

On the fourth hospital day the temperature rose to 105°F, and the patient became incoherent and restless, with muscle twitching. The hematocrit was 56. The chloride was 92 and the potassium 2.5 milliequiv per liter, the nonprotein nitrogen 150, the calcium 7.7 and the blood sugar 308 mg per 100 cc. An electrocardiogram showed a sinoauricular tachycardia at a rate of 125. There were low T waves and moderate left-axis deviation. The chest leads showed a low T wave in Lead CF. The patient was given 20 cc of calcium levulinate without any effect on the muscle twitching. She also received 500 cc of 5 per cent dextrose in physiologic saline solution, 500 cc of whole blood and 2500 cc of 5 per cent glucose in half-strength physiologic saline solution. Nevertheless, she gradually relapsed into coma, and by evening the temperature had reached 106°F. She died on the fifth hospital day.

DIFFERENTIAL DIAGNOSIS

DR WILLIAM W. BECKMAN: This case is a new experience for me because yesterday Dr. Castleman sent the clinical record of this patient to my office and said that I could read it. The record provided really only one datum that is not in the protocol. One gathered from a reading of the record — although it did not state definitely — that a Levine tube had been present in the stomach most of the time that the patient was in the hospital. There was constant drainage from the tube, although the amount is not stated.

DR JOHN B. MCKITTRICK: That is true.

DR BECKMAN: The point about this case that struck me when I first read the record was that the patient apparently had no abdominal pain until six days before entry. Five days before its onset she was examined by a physician who knew her language, — she did not speak English, — and there were no abdominal complaints. She had had a rather abrupt onset of abdominal cramps and apparently went rather rapidly into collapse. X-ray studies revealed obstruction of the sigmoid, which either had become acutely obstructed or, it seems even more probable to me, had perforated and caused peritonitis. I believe that, instead of actual obstruction from a carcinoma, paralytic ileus was present. In any event it is clear that the patient had a carcinoma. There is no question that cecostomy was the indicated step.

The patient was admitted in coma and was known to have an elevated blood sugar, which brings up the possibility of diabetes. Another thing I learned from the record was that there was practically no acetone in the urine. This fact and the carbon dioxide measurements are against diabetic acidosis as an explanation for the coma, indeed, the possibility of diabetic acidosis can scarcely be entertained. The patient probably had the type of acidosis associated with arteriosclerosis in old people, which does not, so far as I know, produce coma. She had diabetes. One cannot be certain, however, how severe the diabetes was because in the hospital she was given injections of glucose that may have contributed to the elevation of the blood sugar.

The significance of the urinary findings is difficult to evaluate. The urine was said to have been normal when the patient was in the outside hospital. She had only one specimen here, which showed casts and albumin and which probably represented a certain amount of kidney disease, probably so-called "vascular nephritis." How much this contributed to the elevated nonprotein nitrogen is difficult to evaluate, because extrarenal factors must be considered.

Another point that was not mentioned in the protocol or the record is that the patient apparently had a fairly adequate urinary output during most of the hospital stay. In spite of this there was

bronchus, near a bronchus or in the lung itself. The nodules in the right lung were well circumscribed in the parenchyma away from the bronchi and were definitely metastatic. We were quite certain that we could rule out bronchiogenic or primary carcinoma of the lung. The bronchial lymph nodes contained no tumor. We searched every organ for a primary source, but we were unable to find any.

The histology of the tumor was typical of what has been described as a mesothelioma (Fig 5). The cells in some areas were cuboidal and arranged around fibrous stalks giving a pseudopapillary pattern. In other areas the cells were large, irregular and closely packed. Some were multinucleated, and others seemed to be forming mucinous material.

A number of papers have been written to the effect that there is no such tumor as mesothelioma of the pleura, that the cells lining the pleura do not form tumors and that these tumors really arise from a small focus in the lung. We have held a similar opinion for a long time. This is perhaps the first case in which we believed that there was actually such a tumor. It certainly fits in with most of the cases of mesothelioma of the pleura that have been reported.*

DR KING: I do not consider that it is fair to have given me a case with a diagnosis against which you, as pathologists, have been talking for twenty years. I could never make Dr Mallory accept a diagnosis of mesothelioma of the pleura.

DR CASTLEMAN: He has been sold on this one. The lesion in the abdomen was retroperitoneal tumor, but there was no tumor elsewhere.

DR ADAMS: What was the large lesion in the left lung?

DR CASTLEMAN: It was merely nodularity due to the pleural tumor.

*Klemperer, P., and Rabin, C. B. Primary neoplasms of pleura. *Arch Pathol* 11:385-412, 1931.

CASE 33112

PRESENTATION OF CASE

A seventy-two-year-old Polish housewife entered the hospital in coma.

Eleven days before entry the patient had received a slight back injury in an automobile accident. A physician examined her at that time and found only slight spasm along the lumbar muscles. Three days later the physician was called again because the patient complained of slight bleeding supposedly from the vagina, he could find no evidence of bleeding. Six days before entry the patient began to have frequent episodes of abdominal cramps. These continued daily. Three days later the abdomen was distended, with marked tenderness and a mass in the right lower quadrant. The patient was taken to another hospital, where a

plain film of the abdomen and a barium enema showed an abrupt, shelf-like obstruction in the lower sigmoid, with a markedly dilated large bowel, particularly on the right, and beginning small-bowel dilatation. Routine urine examinations were said to have been negative. There was a slight leukocytosis, and the blood sugar was 196 mg per 100 cc. On the following day the patient appeared acutely ill. The abdomen was greatly distended, and the patient complained of abdominal pain. No organs or masses could be felt. The pulse was about 115. On the same day an emergency cecostomy was performed under a local anesthetic. There was an increased amount of clear, straw-colored fluid in the peritoneal cavity. The colon and cecum were greatly distended, and a large amount of fluid and gas was removed by trocar suction. A glass Mixer tube was fixed in place by sutures. Following the operation the patient was said to have improved for a while, but the abdominal symptoms subsequently reappeared. She was transferred to this hospital on the afternoon of the second post-operative day.

The patient was known to have hypertension. A sister had diabetes.

Physical examination revealed an obese, disoriented woman. The left border of the heart extended beyond the midclavicular line, but the heart sounds were normal. There were coarse rhonchi, which cleared on coughing, in both lower lobes. The abdomen was distended, tense and slightly tender. Peristalsis was limited to a few tinkles. The diaphragm was high on both sides but moved to percussion. The cecostomy appeared to be functioning well.

The temperature was 100°F, the pulse 120, and the respirations 30. The blood pressure was 110 systolic, 70 diastolic.

A Levine tube was passed immediately on entry, and 500 cc of brownish fluid, as well as considerable gas, was aspirated from the stomach. The patient also received 600 cc of 5 per cent dextrose in water and oxygen. During the night she became extremely disturbed, tore up the oxygen tent and pulled out the intravenous drip and stomach tubes. The cecostomy drained 1680 cc of fluid, and 646 cc of urine was passed on the first hospital day. On the morning of the second hospital day the distention appeared to be slightly less, and peristaltic tinkles were somewhat more frequent. The tongue was dry.

The temperature was 102°F, the pulse 130, and the respirations 30. The blood pressure was 100 systolic, 60 diastolic.

Examination of the blood showed a hemoglobin of 16.3 gm per 100 cc, a hematocrit of 50 and a white-cell count of 9700, with 85 per cent neutrophils. The total protein was 8.5 gm and the non-protein nitrogen 100 mg per 100 cc, the carbon

etermination was made here, but I think that it was everyone's impression who followed this patient that the renal function was reasonably good until terminally, when the urinary output suddenly dropped and the patient excreted practically no urine

CLINICAL DIAGNOSES

Carcinoma of sigmoid, with perforation
General peritonitis

DR BECKMAN'S DIAGNOSES

Carcinoma of sigmoid
Intestinal obstruction (? paralytic ileus or mechanical)
Peritonitis
Mild vascular nephritis
Diabetes mellitus
Severe dehydration
Alkalosis

ANATOMICAL DIAGNOSES

Colloid carcinoma of sigmoid, with perforation and localized peritonitis
(Electrolytic imbalance, with renal insufficiency)

PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY Autopsy showed some of the obvious things that were predicted. There was a carcinoma of the sigmoid, and there was also extensive diverticulosis of the same area. The large bowel was full of feces despite the cecostomy. The peritoneal cavity showed fresh, rather loose adhesions that were probably due to the cecostomy operation a few days earlier. There was no generalized peritonitis. The carcinoma and the area of bowel immediately around it were necrotic and pulled apart in the prosector's hands as he was dissecting it. Although there was a localized sepsis, there was no general peritonitis.

I think that the major question of interest concerns the kidneys in that there seemed to be so much functional evidence of renal insufficiency —

they showed practically nothing. The proximal convoluted tubules were swollen, and occasional loops of tubules revealed albuminous degeneration. It was the extremely mild nephrosis that Fahr* would have described as Grade I nephrosis when he wrote his monograph. I gather from the autopsy findings that the nitrogen retention and other changes were, as Dr Dole suggested, prerenal rather than renal. I do not believe that the renal lesions can even remotely explain the functional findings.

DR BECKMAN I should like to emphasize again that I still believe that the fluid administration was carried out with the proper restraint. I do not believe that one can stress the point too strongly that in a person with high blood pressure and hypertensive heart disease the administration of intravenous fluid and transfusions are apt to cause pulmonary edema. This is due to the development of acute left ventricular failure, with resultant congestion of the lungs.

DR LEONARD P ELIEL What do you think about the administration of 1.8 per cent of physiologic saline solution in a case of this sort to make up the salt deficit and not give too much fluid?

DR BECKMAN I suppose that that would be wiser. I have not had any experience with such therapy.

DR MCKITTRICK I had a rather uncomfortable experience in a similar problem with a chemical imbalance, but in this case there was small-bowel obstruction. The patient was a seventy-five-year-old woman. We gave 1.8 per cent sodium chloride solution, because she had a low chloride, and she went into severe pulmonary edema, which complicated therapy from that point on. Incidentally she also traveled the same path as the patient in the case under discussion. One must be careful about using concentrated saline solution in older people despite the chemical levels.

*Volhard, F., and Fahr, T. *Die Brightsche Nierenkrankheit*. 292 pp. Berlin: Julius Springer, 1914. P. 7.

evidence of marked depletion of the extracellular fluids, on the basis of the marked hemoconcentration shown by the elevated total protein, hemoglobin and hematocrit. There was a low chloride, a low calcium and a low potassium. For some reason there is no mention of the sodium. There was an elevated carbon dioxide content. All these things together indicate that the patient had lost a great deal of fluid from the upper gastrointestinal tract rather than from the cecostomy and that she had an alkalosis as a result of the removal of hydrochloric acid from the stomach.

I suppose that I was given this case to discuss the therapy, but I have always believed that this kind of exercise, in which the case terminates at autopsy, is not a satisfactory way of evaluating therapy. If we were to base an evaluation on such cases we should have to conclude that penicillin was of no value, and that is not quite true. The patient was desperately ill when first seen at the other hospital, and I give credit to everyone for the restrained but expeditious way in which the illness was managed. Every effort was made to correct the various surgical, bacteriologic and chemical abnormalities that were present. A cecostomy was performed to relieve acute large-bowel obstruction. Penicillin was given for what I think was peritonitis. The patient was given sufficient replacement fluid, but with restraint. Another point in the clinical record is that she was seen by Dr. Allan M. Butler, who thought the low potassium represented serious difficulty and suggested the intravenous administration of potassium. There is no way of knowing from the record whether potassium was given.

DR. MCKITTRICK: Potassium was not given.

DR. BECKMAN: It is difficult to administer a significant amount of potassium by vein, for high serum concentrations affect the myocardium and produce ventricular fibrillation. Perhaps with the low value it would have been proper to give a small amount, but potassium must always be given in concentrations not exceeding 4 to 6 milliequiv per liter — the normal value for serum.

DR. MCKITTRICK: I should like to say that Dr. Beckman is a good detective because he deduced all the omissions from the record with exact accuracy. The Levine tube was taken out forty-eight hours before death. His deduction regarding the electrolyte loss is correct, in that for practical purposes all the loss was from the Levine tube. The short history, so far as anyone could determine, is correct. The patient had symptoms for only six days prior to death, they consisted chiefly of abdominal cramps, which began suddenly.

The question of coma on entry is interesting. I did not believe that the patient was in coma. She was moderately irrational, although she did answer questions in her own language. If she was in coma

I do not know what kind, but it certainly was no diabetic coma.

The only blood sugar determinations that indicated a disturbance in glucose metabolism were the ones taken before entry and the one taken at the hospital before intravenous therapy was given. The urinary output was fairly good throughout the hospital stay, with the exception of the last twelve to fourteen hours, when it was markedly diminished — in fact, practically nonexistent. The sodium determination was not done purposely, Dr. Butler, who was called in to see this patient, did not believe that it would help a great deal in planning the treatment. An electrocardiogram was taken in an effort to determine whether there was any evidence of a low potassium, but we could not get any assurance on that score. The report on the determination of potassium came back twenty-four hours later. Despite the low value, Dr. Butler, who was handling that aspect of the therapy, was not quite ready to give intravenous potassium.

My point of view in the treatment of this patient was one of timidity. She was seventy-two years old and had hypertension, she was admitted with a low blood pressure and was probably a senile diabetic patient, as Dr. Beckman has deduced. There was tenderness only over the sigmoid — a point that is not mentioned in either the record or the protocol. At one time we believed that we had induced a certain amount of pulmonary edema with the intravenous therapy. We were cautious about giving potassium, but it may have been needed. All along the line we trailed the patient physiologically, we never did catch up with her. On the night of admission I hesitated to give saline infusion. Whether she should have had saline or something else, I did not know. Peritonitis appeared to be present — I could not understand the small-bowel dilatation, the tremendous dilatation of the stomach or the ileus on any other basis. This was an extremely perplexing problem throughout. All of us see cases like this once in a while, and do not know how to handle them. This is a good case in point because obviously we did not handle the problem correctly. I think that the autopsy findings will either help in the deduction of what should have been done or add further confusion.

DR. VINCENT P. DOLE: The single reported urine specific gravity of 1.026 suggests that the renal function was adequate and that the limitation in renal performance was due to extrarenal circulatory disturbances. It is conceivable that with this infection there was subsequent intrinsic renal impairment. Toward the end the apparently adequate renal output may have been misleading if the kidneys had lost their capacity to concentrate.

DR. MCKITTRICK: Several urine analyses were made at the other hospital. Incidentally, I was the surgeon who did the cecostomy. There was an adequate specific gravity. Unfortunately, only one

chronic illness or other cause and for the establishment of a retirement fund for the full-time employees of the Society. Furthermore, the report recognized the need of the Boston Medical Library for financial assistance and expressed the opinion that the library is an asset of the Society that should not be lost. In view of these facts, the committee recommended that the annual dues be increased to \$20.00, with the possibility that they might eventually be raised to \$25.00. The Executive Committee of the Council had approved the report and had made the following recommendations: that the annual dues for regular members be raised to \$25.00, that the rate become effective on January 1, 1948; and that of this sum, \$5.00 be earmarked for the Boston Medical Library. After a relatively short discussion, these recommendations, with two minor amendments, were adopted.

MORE PROTEIN FOR PREMATURE INFANTS

THE care of the premature infant constitutes, in pediatric practice, a particular problem by itself, with faithful attention to detail as the usual price of success. Three cardinal principles, with their ramifications, have long been recognized. These are maintenance of a suitable external environment, with special reference to temperature and oxygen content, protection against infection and suitable nourishment.

The necessity for the first two is in every case immediate, the third cannot be long delayed, and its problems are receiving renewed attention with recognition of the possibility that human milk is not necessarily the ideal food for the premature infant, regardless of the value it may have for the full-term infant.

Three Swedish investigators, Jorpes, Magnusson and Wretling,^{1,2} recognizing that the infant born several weeks before term has different nutritional requirements from the full-term newborn infant, have devised a supplementary food consisting of all the essential amino acids. The mixture used, made by the enzymatic hydrolysis of casein with pancreatic ferments, was added to human milk and in every case was followed by considerably greater gains in weight than those that were obtained with human

milk alone or when supplemented by unhydrolyzed casein.

Although these reports are among the first on the direct use of the amino acids to improve weight gain of premature infants, other writers have recognized the unusual needs of these patients for extra protein, calcium and phosphorus. Thus, Gordon and Levine,³ in 1944, stressed the wide variability in the nutritional needs of individual infants, whether breast or artificially fed, and pointed out the relative inability of premature infants to absorb fat, as evidenced by their frequent excessive loss of calories in the form of fecal fat. Not only are they apparently unable to utilize much fat, in which human milk is rich, but also they especially need protein, calcium and phosphorus, in which human milk is relatively low.

The implication is obvious: human milk, designed by Nature as a suitable food for the average full-term infant, must not be dogmatically and doggedly urged as the ideal food for all infants. Otherwise its employment needs no such unusual defense or apology as was offered by the medical student who, when required in an examination to state three particulars in which human milk is superior to cow's milk, wrote that it is cleaner, that it is more digestible and that it comes in more attractive containers.

REFERENCES

1. Jorpes J. E., Magnusson J. H., and Wretling A. Casein hydrolysate for premature infants. *Lancet* 2:228-232, 1946.
2. Magnusson J. H. Use of amino acid mixture (casein-hydrolysate) as supplementary feeding for prematures during first weeks of life. *Acta paediat* 32:599-625, 1945.
3. Gordon H. H. and Levine S. Z. Metabolic basis for individualized feeding of infants, premature and full term. *J. Pediat* 25:464-475, 1944.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

BACTERIOLOGICAL LABORATORY MOVES

The Bacteriological Laboratory of the Massachusetts Department of Public Health has been moved from the State House and is now established in its new quarters at the old Bussey Institute building near the Arnold Arboretum. All requests for bacteriologic outfits and all specimens should be addressed to the State Diagnostic Laboratory, 281 South Street, Jamaica Plain 30. The telephone is ARNold 5440.

OFFICIAL OPENING OF NEW BLOOD PROCESSING LABORATORY

The Division of Biologic Laboratories of the Massachusetts Department of Public Health will have open house on March 26 in conjunction with

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Established 1828

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COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

FEBRUARY MEETING OF THE COUNCIL

A STATED meeting of the Council of the Massachusetts Medical Society was held at the Boston Medical Library on February 5. Several matters of immediate interest to all members of the Society were discussed and duly acted on.

In the first place, the recommendation of the Committee to Nominate a Director of Medical Information and Education that Dr. John F. Conlin be appointed to this position was unanimously adopted. Dr. Conlin, who is thirty-eight years old, spent from 1926 to 1932 in a monastic order, he graduated from Boston College in 1934 and from Tufts College Medical School in 1938. After an internship at St. Elizabeth's Hospital and a residency at John Adams Hospital in Chelsea, he entered the Army in 1942 and was discharged

with the rank of colonel in 1946. During the last session of the Legislature he was extremely helpful in the fight against the Anti-Vivisection Bill. All in all, it appeared to the members of the committee that Dr. Conlin was highly qualified, by training, experience and attainment, for the new position, and the Council concurred. He is now attending courses at the Harvard School of Public Health and will assume office on or about July 1.

The second matter of importance concerned a recommendation by the Committee on Public Health that aggressive support be given to Commissioner Getting's program for improving conditions in state and local public-health departments. His proposals included higher salary levels for the professional personnel, the institution of a sanitary code, the subsidization of local health departments that meet established standards and the promotion of town unions of sufficient size to ensure support of modern public-health programs. The acceptance of this recommendation had not been approved by the Executive Committee of the Council, apparently because it was thought that the Society had no right to recommend salary increases for a particular group of physicians, and several councilors spoke in the same general vein. The discussion was concluded by Dr. Getting, who clearly outlined the difficulties that state and local health departments were encountering because of the inadequate salaries paid to professional workers and predicted a marked deterioration of such services unless something were done in the immediate future. He added that this directly concerned the health of the people of the Commonwealth, and that because of this, his program should be supported by the Society. The recommendation was approved by the Council with only a few dissenting votes.

Finally, the report of the Committee to Study Increase in Assessment of Dues was presented. It was brought out that the activities of the Society had greatly increased in recent years and that the sum needed to pay full-time and part-time salaries had proportionately grown. Attention was called to the need for a permanent headquarters for the Society, for some fund to aid the widows and children of deceased physicians, for one to help financially physicians who are incapacitated by

The New England Journal of Medicine

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Volume 236

MARCH 20, 1947

Number 12

SECOND-DAY ENCEPHALOGRAPHY, WITH PARTICULAR REFERENCE TO THE SIZE OF THE VENTRICLES*

RICHARD SCHATZKI, M.D.,† DONALD H. BAXTER, M.D.,‡ AND CHARLES E. TROLAND, M.D.§

THE literature contains a comparatively small number of publications concerning the appearance of the ventricles on the days following encephalography, although it is quite probable that a number of investigators have been interested in such follow-up studies without publishing them. Of the published reports, some were confined to the rate of absorption of air after encephalography,^{1,2} whereas others emphasized the importance of second-day studies for the demonstration of porencephalic cysts.^{3,4} Only a few observations were concerned with the size of the ventricles during follow-up studies, and those were quite contradictory. Schott and Eitel,⁵ as well as Reinberg,⁶ mention dilatation of the ventricles in later films as if it were a routine finding. This broad statement is made without any supporting evidence, no actual encephalograms are reproduced to illustrate this so-called "routine second-day enlargement." The explanation of Davidoff and Dyke¹—that these authors mistook the better visualized anterior horns for enlarged ventricular bodies—appears quite plausible. Friedman, Snow and Kasanin⁷ state that the shape of the anterior horns usually changes on the second day from the butterfly pattern to a more or less rounded form because of transitory internal hydrocephalus. This observation can apparently be explained on a basis similar to that mentioned by Davidoff and Dyke,¹ who state that there is no enlargement of the ventricles on the second day. Evans⁸ reported follow-up studies in 39 children, the majority of whom showed a slight increase in the size of the ventricles on later examination. In 7 cases there was a more striking increase in the size of the ventricles on the second day. Paul and Erickson,³ in a recent publication concerning second-day studies in 78

patients, found the ventricles usually decreased. Seven of the patients, however, showed an increase in the size of the ventricles on the second day. It was interesting to find that 4 of the 7 cases were post-traumatic, whereas 2 were cases of idiopathic epilepsy and 1 was a case of Alzheimer's disease.

During our encephalographic studies in a series of head injuries, some abnormalities were found that

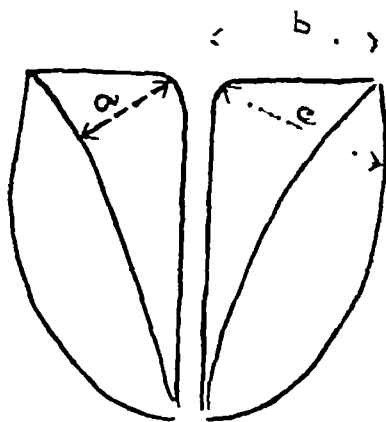


FIGURE 1 Ventricular Measurements in the Anteroposterior View

The measurement of the width of the ventricle (a) was considered the most important of the measurements, it is the shortest distance between the lateral wall of the ventricular body and the superior medial corner of the ventricle.

led to a systematic examination of the skull on the days following the lumbar insufflation of air. We found definite enlargement of the ventricular bodies in a third of the group, the enlargement being extensive in some cases.

MATERIAL AND METHODS

Patients Examined

Among a large group in which encephalography was done, second-day studies were performed in 67 cases. In 60 cases, in which examination on the first

*Presented at the annual meeting of the Massachusetts Medical Society, Section of Radiology, Boston, May 23, 1946. Material collected at McGuire General Hospital, Richmond, Virginia.

†From the Department of Radiology, Massachusetts General Hospital, Boston; the Shreveport Hospital, Shreveport, Louisiana; and the Medical College of Virginia, Richmond, Virginia.

‡Instructor in roentgenology, Harvard Medical School, radiologist, Massachusetts General Hospital.

§Senior resident in radiology, Shreveport Hospital.

Assistant professor of neurologic surgery, Medical College of Virginia, associate neurosurgeon, Medical College of Virginia Hospital.

the formal dedication of the Blood Processing Laboratory at 375 South Street, Jamaica Plain

Official opening of the Blood Processing Laboratory, the first state-operated laboratory designed specifically for large-scale blood processing and fractionation, will give physicians and others an opportunity to see in operation the equipment, methods and technics involved in mass production of blood derivatives. Staff doctors and technicians will be at hand to explain the work and to furnish any pertinent information desired by visitors. Glass-paneled refrigeration, sterilizing and filling rooms make it possible for onlookers to observe each part of the processing without the necessity of entering these rooms.

Although the occasion is primarily for the dedication of the new laboratory, the Antitoxin and Vaccine Laboratory will also be open to accommodate those who are interested in the preparation of the serums, vaccines and antitoxins that are manufactured there for distribution throughout the Commonwealth.

Open house will be held during the morning from 9 00 to 12 00, and in the evening from 6 00 to 9 00. Conducted group tours will be part of the activities of the day.

A cordial invitation to visit the laboratories is extended to all.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Nitrous Oxide-Oxygen Anesthesia. McKesson-Clement viewpoint and technique. By Major F W Clement, MC, A US, anesthetist to Toledo, Mercy and St Vincent's hospitals, Toledo, Ohio. Second edition, thoroughly revised. 8°, cloth, 288 pp., with 92 illustrations. Philadelphia: Lea and Febiger, 1945. \$4 50.

This new edition has been revised in the light of knowledge gained during World War II. During the period there have been no radical changes in either the agents used for anesthesia or their methods of administration, but much has been learned of the physiology of lowered oxygen tensions encountered in aviation. In this revised edition the changes are those of details rather than alterations of the original text. Changes and additions include the commonly accepted theory of nitrous oxide-oxygen anesthesia, with greater detail of its method of administration, the possible dangers associated with prolonged oxygen deficiency, the mechanism and treatment of shock, the role of carbon dioxide and of the sino-aortic areas and the compensatory reflex mechanism that protects the body in the presence of lower oxygen intake. The chapter on dental anesthesia has been enlarged to include more details on the use of the nasal-pharyngeal airway. This is a comprehensive monograph on its subject.

New Goals for Old Age. Edited by George Lawton. 8°, cloth, 210 pp. Second printing. New York: Columbia University Press, 1945. \$2 75.

This composite work brings together the various social and medical aspects of old age. The material was originally delivered as lectures in a course on mental health and old

age, under the Section on the Care of the Aged of the Welfare Council of New York City, during 1940-1941. The lectures are here brought together for the first time. An interesting final chapter is contributed by an aged woman who spent some of the happiest years of her life in a home for the aged. She is nearly eighty years old and entitles the chapter, "How it feels to be seventy-five and a woman." A bibliography of fifteen pages is appended to the text.

Bacillary Dysentery, Colitis and Enteritis. By Joseph Felsen, MD, director of medical research, Bronx Hospital, New York, and director, International and Pan-American Dysentery Registry. 12°, cloth, 618 pp., with 145 illustrations. Philadelphia: W B Saunders Company, 1945. \$6 00.

This monograph presents a correlated study of the historical, epidemiologic, clinical, pathological, bacteriologic, serologic and therapeutic aspects of bacillary dysentery. Dr Felsen is an authority on the subject, having dealt with epidemics, as well as clinical cases in their various manifestations. He established the International Dysentery Registry as a means of promoting co-ordinated study and preventive activity. He divides his subject into two main sections dealing with the acute and chronic forms of the disease and including chronic ulcerative colitis and chronic distal ileitis. An appendix is devoted to the technical methods used in the diagnosis of the disease. The last part of this chapter considers the prevention and control of bacillary dysentery and other infectious diarrheas. This is the first comprehensive study on the subject published in the United States. An extensive bibliography of ninety-six pages is appended to the text. This monograph should be in all medical libraries and in the libraries of physicians interested in the disease.

NOTICES

ANNOUNCEMENT

Dr Armand M Gamboa announces the removal of his office to 475 Commonwealth Avenue, Boston.

SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the Sheltered Workshop of the Boston Tuberculosis Association, 35 Tyler Street, Boston, on Tuesday, March 18, at twelve noon. Dr John Homans will speak on "Arterial Deficiencies in the Legs in Middle and Advanced Age."

Physicians are cordially invited to attend.

AMERICAN COLLEGE OF CHEST PHYSICIANS

The oral and written examinations for fellowship in the American College of Chest Physicians will be held at Atlantic City on June 5. Applicants for fellowship in the College who plan to take these examinations should communicate at once with the Executive Secretary, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10.

The thirteenth annual meeting of the College is scheduled to be held at the Ambassador Hotel, Atlantic City, June 5 to 8. The convocation for new fellows and life members of the college will be held on the first day of the meeting, when certificates will be awarded to fellows and life members admitted since June, 1946.

PRIZE CONTEST

The American Association of Obstetricians, Gynecologists and Abdominal Surgeons recently announced that the annual prize contest will be conducted again this year. Requests for detailed information should be addressed to the secretary, Dr James R Bloss, 418 Eleventh Street, Huntington 1, West Virginia.

(Notices continued on page xix)

entral ray in the vertical position. Anteroposterior, posteroanterior and lateral stereoscopic views represented the routine examination, additional films were taken in individual cases. The tube-film distance was held constantly at 90 cm, the projection in various positions was standardized as much as

cedures. On the basis of past experience, the size was first judged without measurement. The ventricles were classified as normal, moderately enlarged and enlarged and were then measured. Whenever possible the following separate measurements were made on the anteroposterior projection with

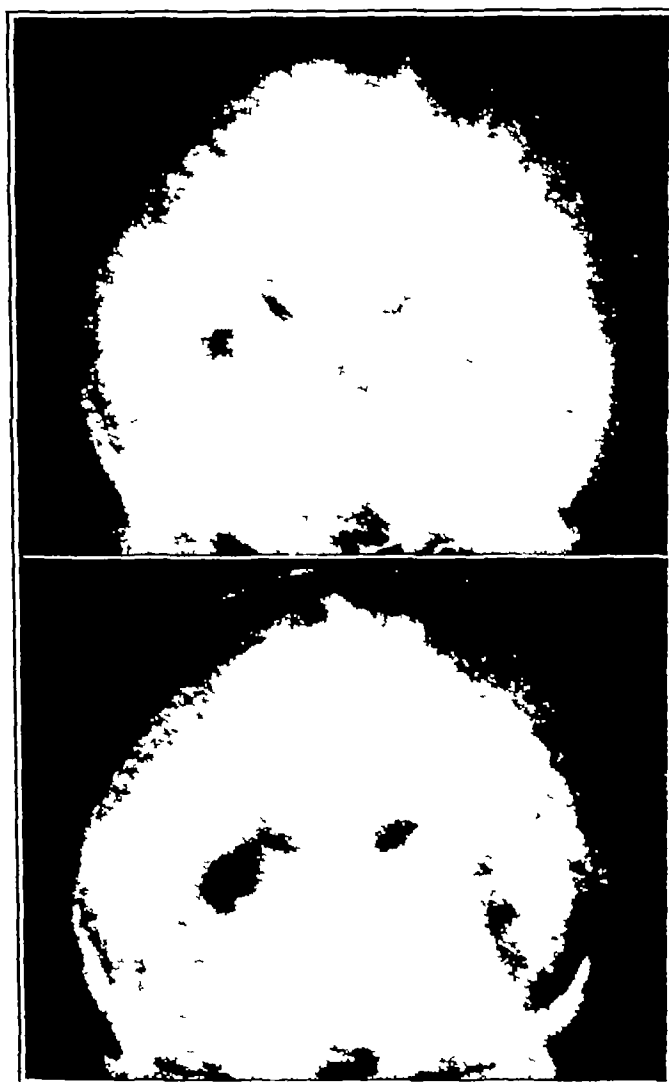


FIGURE 3 Case 1.
These films are first-day (upper) and second-day (lower)
posteroanterior views

possible. The first examination was made in the early hours of the afternoon. The second-day examination was usually done sometime during the forenoon, so that the actual time elapsed between the two examinations was between eighteen and twenty-two hours.

Various methods of measuring ventricles have been devised.^{1, 2, 3} We used two different pro-

cedures. In the horizontal position the distance between the superior medial corner of the ventricle and the convex lateral border of the ventricular body (Fig 1a), the distance between the superior medial corner and the superolateral corner of the ventricle (Fig 1b), and the distance between the superior medial corner of the ventricle and the concave lateral wall of the anterior horns (Fig 1c)

day was satisfactory and allowed comparison for follow-up studies, 35 patients had had open and 8 had closed head injuries and 7 had epilepsy, in 10, the examination was performed for other causes. In other words, a history of head injury was present in about two thirds of the cases. The interval between

30 to 45 cc of a 2.5 per cent solution being administered intravenously. The patient started to become active toward the end of, or immediately after, the completion of the examination. Two needles were introduced into the lumbar canal in two adjacent interspaces. About 20 cc of fluid was removed and



FIGURE 2 Case I

The lower film, an anteroposterior view taken on the second day, shows enlargement of both lateral ventricles, compared with almost normal-sized ventricles on the first day. There was a history of trauma four times in eight years, all of them due to automobile accidents, the last having occurred five months previously. There had been rapid mental deterioration for four months. Two hundred and forty cubic centimeters of air was injected. Clinically the patient was suspected of having brain atrophy, and the appearance of the ventricles on the second day corresponded with the clinical picture.

injury and encephalography, which varied from case to case, was over five months in approximately two thirds of the cases.

Methods of Examination

The patient was usually prepared with 10 mg of morphine and 0.4 mg of scopolamine. The examination itself was performed under Pentothal anesthesia,

replaced by the same amount of air. This procedure was repeated until a dry tap was obtained. The total amount of fluid removed varied, of course, from case to case. Its importance in relation to the second-day enlargement of the ventricles is discussed below.

Routine roentgenologic examination was done with the patient in the horizontal position and the

entral ray in the vertical position. Anteroposterior, posteroanterior and lateral stereoscopic views represented the routine examination, additional films were taken in individual cases. The tube-film distance was held constantly at 90 cm, the projection in various positions was standardized as much as

cedures. On the basis of past experience, the size was first judged without measurement. The ventricles were classified as normal, moderately enlarged and enlarged and were then measured. Whenever possible, the following separate measurements were made on the anteroposterior projection with

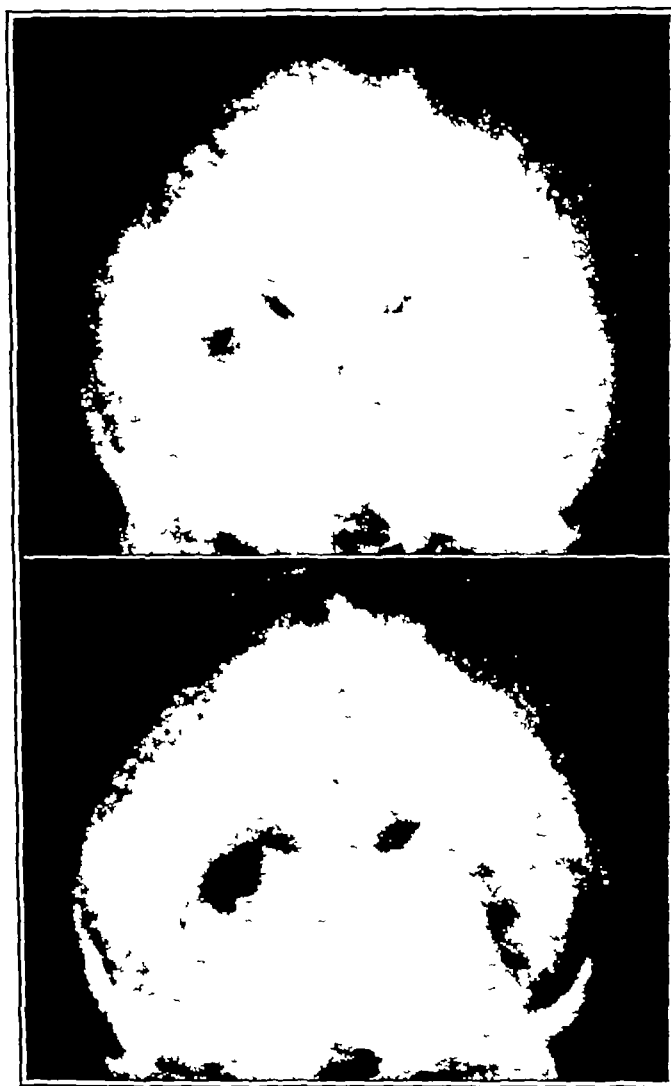


FIGURE 3 Case 1.

These films are first-day (upper) and second-day (lower) posteroanterior views.

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Various methods of measuring ventricles have been devised.^{1, 2, 9} We used two different pro-

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The last line formed an angle of approximately 30° with the horizontal, it was at times difficult to measure and, if so, was quite arbitrary

Like Paul and Erickson,³ we found the first measurement to be of particular significance for the actual size of the ventricles, whereas the others were

(Fig 1a) was 1.1 cm or less as normal, 1.2 cm to 1.4 cm as usually normal, 1.5 cm as borderline, and 1.6 cm as dilated. These standards were of course somewhat arbitrary, but for comparative studies they were found to be quite satisfactory. The influence of a slight variation in projection on the size



FIGURE 4 Case 2

These films show increased ventricular enlargement two days following encephalography (no films were taken on the first day following the first examination). There was no history of injury. The patient had experienced disorientation and mental confusion for six weeks. There had been slight transient papilledema. One hundred and forty cubic centimeters of air was injected. The diagnosis was brain atrophy.

at times helpful in cases of localized loss of brain substance. The decision regarding the normal limit of the size of the ventricle is of necessity arbitrary in borderline cases, in spite of studies made in large groups of probably normal encephalograms.^{1, 8} After a time, our estimated enlargement and that shown by actual measurement coincided fairly well, although in borderline cases there were some differences. We considered a ventricle whose width

of the ventricles was checked in a number of cases. It was found to have a marked influence on the "height"¹⁰ of the ventricles but produced only negligible differences in the measurements used.

RESULTS

Size of Ventricles

Of the 60 cases in which comparative second-day measurements were possible, the ventricles were

found to be larger on the second day in 23 (38 per cent). The enlargement was usually seen in the anteroposterior, posteroanterior and lateral projections but it was most easily recognizable in the anteroposterior projection (Figs 2, 3, 4, 5 and 6). In 18 cases, the second-day enlargement was con-

group of cases showed some enlargement of the ventricles on the second day, whereas approximately 8 per cent of the total group showed marked enlargement. Of 43 patients who had suffered closed or open head injuries, 18 showed some enlargement. All the cases with pronounced second-day enlarge-

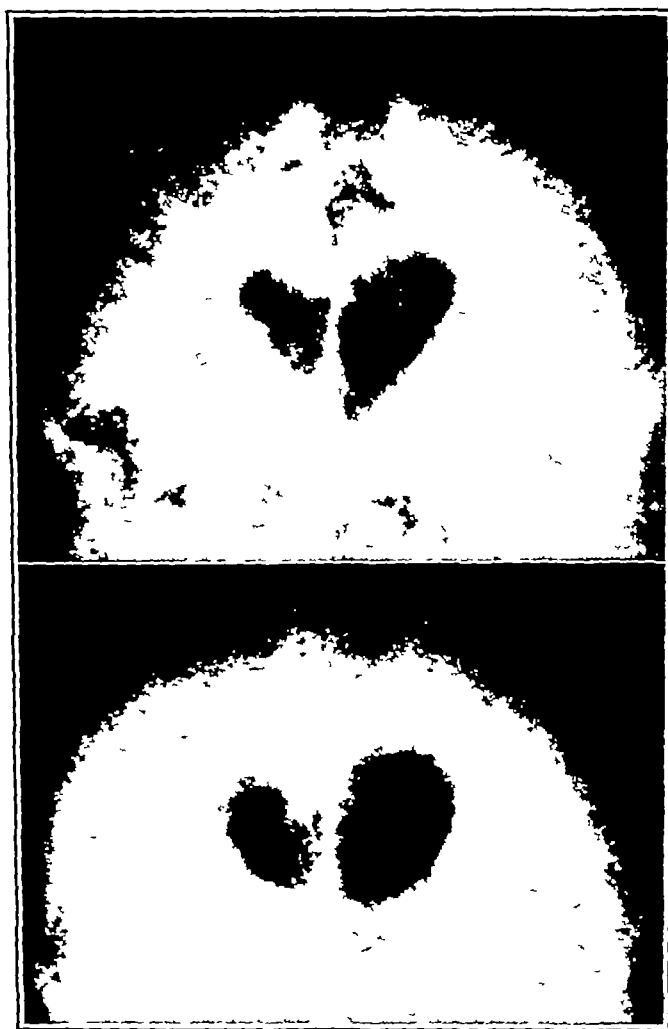


FIGURE 5 Case 3

These films, which are anteroposterior views, show obvious second-day increase in ventricular enlargement. The patient had been struck on the head by a baseball six years before and was unconscious for eight days. He had had generalized convulsions for the previous five years. Neurologic examination was negative. Two hundred and ten cubic centimeters of air was injected.

sidered to be slight, whereas in 5 a marked increase in the size of the ventricles occurred in the twenty-four-hour period. A slight decrease was seen in 3 cases. In 12 cases, there was no appreciable change in the size of the ventricles on the second day, and in 22 the amount of air in the ventricles on the second day was not sufficient for measurement. In other words, slightly more than a third of the total

ment fell into the group with head injuries. In brief, of the patients with head injuries approximately 42 per cent showed some second-day enlargement of the ventricles and in 12 per cent of these the enlargement was marked.

It is interesting to compare our findings with those of Paul and Erickson.² Our technic was slightly different from theirs, inasmuch as our studies

were made with the patient in a horizontal and not in a vertical position. Only a few of our cases showed any reduction in the size of the ventricles, and the degree of decrease was not striking. It is likely that in many of our cases in which measurement in the horizontal position was not possible on the second day the ventricles would have been decreased in the upright position. The smaller percentage of

encephalographic material. Our impression is that its incidence will be fairly high in any group of cases with cerebral atrophy.

Information about the amount of spinal fluid drained at the time of encephalography was available in 36 cases of the group. In 26 cases, less than 150 cc had been drained. Second-day enlargement was slight in 6 and marked in 3. Of 10 cases in which



FIGURE 6 Case 3
These films are left lateral views on the first and the second day

second-day enlargement noticed in the material presented by Paul and Erickson³ may be partially attributed to the difference in the position of the patient, but was more probably due to the fact that only 18 per cent of their cases were post-traumatic, as compared with 71 per cent in our series. In this connection, it is noteworthy that of the 7 cases in which Paul and Erickson found second-day enlargement, there had been trauma in 4. Thus, second-day enlargement is obviously more frequent in post-traumatic patients than in the routine average

more than 150 cc had been drained, 4 patients showed slight and 2 marked second-day enlargement. In other words, the incidence of second-day enlargement was slightly higher if more than 150 cc of cerebrospinal fluid had been obtained.

In addition to the striking increase in the size of the ventricles, abnormalities observed in some of the cases made the second-day study worthwhile. The importance of the demonstration of porencephalic cysts has been emphasized by Pendergrass and Hodes,⁴ as well as by Paul and Erickson.³ In 3

of our cases the cyst was visible only on the follow-up film, whereas in 4 others the cyst, although visible at the original examination, was better filled on the second-day examination (Figs 7 and 8). In addition to the better demonstration of porencephalic cysts, second-day examination is considered

in the appearance of the septum is difficult to explain. At times it was purely an optical phenomenon, since different parts of the wavy septum were demonstrated on different days of the examination. At other times, however, the septum actually seemed to bulge markedly on the second



FIGURE 7 Case 4

The lower film, taken six days after the first examination, shows filling of a porencephalic cyst (no intermediate examinations were made). Note the defect of the frontal bone and the displaced bone fragments deep inside the vault. The patient had had a right frontal injury by a shell fragment two months previously, with immediate débridement. There was loss of memory and poor cerebrations. One hundred and forty cubic centimeters of air was injected.

of value in cases in which only one ventricle was filled on the first day and in which, by proper positioning of the head, filling of the other ventricle was obtained on the second-day examination.^{3,4}

In 8 of our cases a bulging of the interventricular septum was noted on the second-day roentgenograms (Fig 9). This was either not present or much less pronounced on the original films. The change

day, whereas it had been absolutely straight on the first day. It is likely that this is evidence of a change in the shape of the ventricles from day to day, the ventricles being not so fixed in size and shape as they are usually assumed to be. Septal bulging was found only in patients with dilated ventricles, and it is likely that the shape of the ventricles is particularly variable in patients with brain atrophy. In

7 cases the septum bulged toward the right side. There was no obvious relation between the side of maximum brain loss and the direction of the bulge.

DISCUSSION

The increase in the size of the ventricles in some of our cases was quite unexpected. Although the

follow-up examination, this was not always accomplished. A slight change in projection, however, caused no appreciable enlargement of the width of the ventricles, as we proved in especially conducted studies. In addition, a definite increase in the size of the ventricles on the second-day examination was found in cases in which the projections on the two

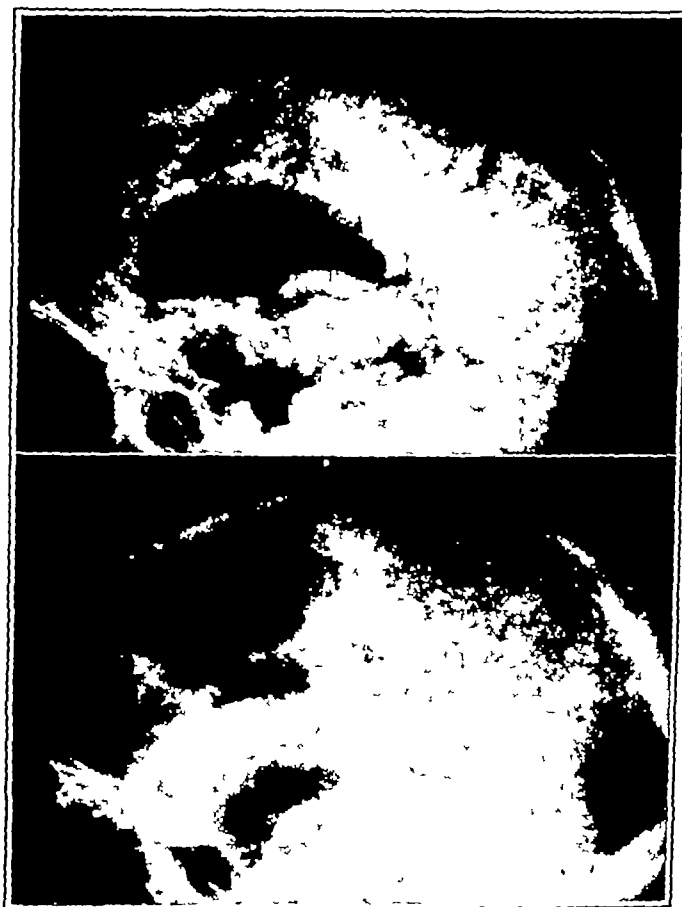


FIGURE 8 Case 5

The lower film demonstrates second-day filling of a porencephalic cyst. Note the air-filled cyst above the dilated anterior horn. The patient had had a left frontoparietal injury due to grenade fragments and followed by debridement. There had been marked aphasia, which had improved. There was an old papilledema, with diminished vision, as well as slight headache and dizziness. The brain protruded through the skull defect, and most of the porencephalic cyst was within the protrusion. One hundred and eighty cubic centimeters of air was injected.

observation appears to be irrefutable, the explanation is difficult and debatable. An explanation on a purely optical basis can be excluded. The various examinations were performed under identical circumstances, and the same optical conditions existed. The size of the frontal sinuses was measured routinely and was found to be identical in the different examinations of a given case. Although an attempt was made to reproduce the original projection in the

examinations were identical. In short, there can be no doubt that the ventricles in these cases were larger on the second day.

The question arises regarding the correct size of the ventricles in such cases. Were the ventricles on the first-day examination smaller than they normally are, or was there a transient abnormal increase in their size on the day following the introduction of air? Paul and Erickson² apparently as-

sume that the second-day dilatation is the artificial finding and give the following possible explanations: Gas, trapped at the base of the skull — in the cervical region, the cisterna magna or the subarachnoid space of the posterior fossa or even in the third or fourth ventricle — passed upward. This explanation appeared to be applicable to some of our cases. Rapidly emptying gas from the subarachnoidal space

that the brain responds rapidly to decreased intracranial pressure by an increase in volume. Such increase may be due to either edema or hyperemia of the brain. One may assume that the sudden withdrawal of all the ventricular fluid represents a marked trauma to the brain which quickly responds to such trauma. In other words, the enlarged brain presses from all sides on the ventricles and de-



FIGURE 9 Case 6

The lower film shows the second-day bulge of the septum pellucidum. The patient had had grand-mal attacks for four years, but there was no history of trauma.

caused dilatation of the ventricles. An abnormality was present in the gaseous interchange between the air in the ventricles and the gases in the cerebral tissues or blood vessels. Finally, a difference in the intracranial pressure for the two days or, to a lesser extent, in the temperature altered the gas volume.

In our opinion, it is difficult to say whether the size on the first or the second day represents the normal condition of the ventricles. It is well known

increases their size. Within twenty-four hours the irritation caused by the sudden withdrawal of fluid subsides and the ventricles resume their normal size. In favor of this assumption is the fact that in patients in whom films were taken after twenty-four hours, no further increase in the size of the ventricles was noted. This theory also explains why, in a few cases of severe, repeated brain trauma with clinical signs of considerable brain damage, the ventricles

7 cases the septum bulged toward the right side. There was no obvious relation between the side of maximum brain loss and the direction of the bulge.

DISCUSSION

The increase in the size of the ventricles in some of our cases was quite unexpected. Although the

follow-up examination, this was not always accomplished. A slight change in projection, however, caused no appreciable enlargement of the width of the ventricles, as we proved in especially conducted studies. In addition, a definite increase in the size of the ventricles on the second-day examination was found in cases in which the projections on the two



FIGURE 8 Case 5

The lower film demonstrates second-day filling of a porencephalic cyst. Note the air-filled cyst above the dilated anterior horn. The patient had had a left frontoparietal injury due to grenade fragments and followed by debridement. There had been marked aphasia, which had improved. There was an old papilledema, with diminished vision, as well as slight headache and dizziness. The brain protruded through the skull defect, and most of the porencephalic cyst was within the protrusion. One hundred and eighty cubic centimeters of air was injected.

observation appears to be irrefutable, the explanation is difficult and debatable. An explanation on a purely optical basis can be excluded. The various examinations were performed under identical circumstances, and the same optical conditions existed. The size of the frontal sinuses was measured routinely and was found to be identical in the different examinations of a given case. Although an attempt was made to reproduce the original projection in the

examinations were identical. In short, there can be no doubt that the ventricles in these cases were larger on the second day.

The question arises regarding the correct size of the ventricles in such cases. Were the ventricles on the first-day examination smaller than they normally are, or was there a transient abnormal increase in their size on the day following the introduction of air? Paul and Erickson² apparently as-

ARTHRITIS IN THE MEDITERRANEAN THEATER OF OPERATIONS*

II. Clinical Description of Hypertrophic Arthritis, Arthralgia and Psychogenic Rheumatism

LIEUTENANT COLONEL CHARLES L. SHORT, MC, AUS

THE types of joint disease often encountered in the Mediterranean Theater, in addition to rheumatoid arthritis, which was discussed in a previous paper,¹ included hypertrophic arthritis, arthralgia and similar disorders, and psychogenic rheumatism

HYPERTROPHIC ARTHRITIS

The aspects of hypertrophic arthritis that seemed of importance in the Theater are covered in this section, no attempt being made to discuss the definitive treatment of the disease. Because it was usually employed, the designation "hypertrophic arthritis" is used throughout to avoid confusion, although in some ways its synonyms, such as "degenerative joint disease" and "osteoarthritis," are preferable. When possible, the two types of hypertrophic arthritis encountered in military as well as in civilian practice are differentiated and compared. These are the primary usually more generalized type and the secondary more localized type, resulting from structural abnormality, previous trauma or joint damage caused by another form of arthritis.

Incidence

The exact incidence of hypertrophic arthritis in the Theater could not be determined. A total of 621 cases were reported by questionnaires from ten general hospitals. This figure may be somewhat higher than the actual one because of both duplication of cases and a tendency to diagnose the disease from x-ray findings when it might not be responsible for the patient's disability. Hypertrophic arthritis made up about 25 per cent of the total number of patients with arthritis admitted to general hospitals, a ratio approximating that found by Boland and Corr² in a general hospital in the United States. The prevalence of this disease, which is generally regarded as an affection of middle or old age, in an overseas theater seems unusual until the large number of soldiers in their late thirties are taken into account as well as the still older commissioned and noncommissioned officers of the higher grades. In addition, the secondary type, which is usually symptomatic at an earlier age, made up over a third of the cases diagnosed as hypertrophic arthritis.

Etiology

Table 1 presents the age distribution of 51 cases of hypertrophic arthritis, with a comparison between primary and secondary types. The mean age of the primary type, forty-one years and eight months, sur-

passed by about ten years that found for a series of patients with rheumatoid arthritis.¹ In spite of the small number of cases, a significant difference also seemed to exist between the two forms of hypertrophic arthritis, since the majority of cases in the primary type occurred in the fifth decade of life in comparison with the fourth decade in most of the other group.

The cause of the primary type of hypertrophic arthritis remains unknown, although aging and degeneration of articular cartilage certainly constitute the underlying process. Other etiologic factors are therefore difficult to assess, although exposure to cold and dampness, sleeping on the ground and the strain of long marches, especially in mountainous country, and of riding in army vehicles were all cited by patients as precipitating causes of disabling symptoms. Acute trauma to a joint in the form of a strain or a direct blow from a fall also preceded the onset in certain cases or caused an acute exacerbation in a previously mild process. All these factors were also operative in bringing patients with the secondary type to medical attention, although the underlying process was usually initiated years previously. Table 2 lists a classification of the factors apparently causing or accelerating the development of the secondary type of hypertrophic arthritis. These data were derived from the records of 100 such patients in a combined series of 270 cases in which the diagnosis was made. A study of the table reveals that trauma was a cause about three times as frequently as a long-standing or congenital structural abnormality. The types of trauma were about equally divided between an actual fracture, either ununited or healing in a position to throw strain on one or more joints and direct or indirect trauma to the joint itself. One patient developed hypertrophic arthritis of the shoulder joint secondary to the continued presence in the joint of shot-gun pellets, acquired four years previously. This case, together with others previously reported, points to the importance of the removal of missiles or shell fragments from joints to prevent what has been called "foreign-body arthritis."

Diagnosis and Clinical Features

From the data given above regarding age incidence and from the general experience in the Theater, hypertrophic arthritis was naturally suspected when an older patient presented himself with joint complaints. A previous history of similar symptoms, usually low-grade, was frequently obtained especially in response to unfavorable climatic conditions or unusual exertion. In many cases there

*The following material represents a condensation and a certain amount of revision of parts of a clinical monograph on arthritis prepared at the direction of the Surgeon, Mediterranean Theater of Operations, United States Army and submitted to him in final form in June 1945.

appeared normal, or almost normal, on the first day and showed dilatation on the second day. This second-day dilatation of the ventricles coincided better with what had been expected from the clinical picture.

On the other hand, it is conceivable that the first-day examination represented the normal size of the ventricles and that the irritation of the air in the ventricles caused hypersecretion to such a degree that it was inadequately drained through the foramina of the fourth ventricle and thus led to dilatation of the ventricles. In favor of this theory, is the fact that the second-day enlargement was generally seen if large amounts of air had been introduced. The evidence against this theory, however, is stronger than that in favor of it. In some cases the ventricles not only were larger on the second day but also contained more air than on the first day. Hypersecretion, with an increase of the pressure within the ventricles, should press the air out into the subarachnoid space and should not attract it.

Measurements of the cerebrospinal-fluid pressure at the time of introduction of air and again on the day following the encephalography would be interesting. The latter measurements were not made in this series.

Although a satisfactory explanation of second-day enlargement is not possible, we are inclined to believe that if the ventricles enlarge within twenty-four hours, the second-day examination represents the normal or resting size. Further clinical and experimental studies regarding this problem appear to be necessary.

There are certain practical applications of the recognition of this phenomenon. We have not seen pronounced second-day enlargement in cases without fairly marked clinical evidence of brain damage. For this reason, routine study of the ventricles twenty-four hours after the introduction of air is advised. This study is particularly indicated in cases with old head injuries or in those in which atrophy from other causes is suspected. The second-day examination not only often shows bilateral or unilateral dilatation that was not present on the first day but also, at times, emphasizes and clarifies certain anomalies that were equivocal on the first

day. We have seen a few cases in which the second day examination clearly showed the presence of brain atrophy, whereas that on the first day had left the question of tumor or atrophy open.

SUMMARY

Observations in 60 patients who had roentgenologic studies on the day following routine encephalography are described. Thirty-five of these had open and 8 had closed injuries, 7 were epileptic, and in 10 the examination was performed for other reasons.

A slight decrease in the size of the lateral ventricles on the second day was seen in 3 cases. The lateral ventricles were slightly larger on the second day in 18 cases, and there was marked enlargement in 5 cases. Each of the last cases had a history of preceding head injury.

At times, a peculiar bulging of the interventricular septum was seen on the second day. Second-day studies showed filling of porencephalic cysts that were not filled, or incompletely filled, on the first day.

The mechanism of second-day enlargement is discussed.

Roentgenologic studies on the day following encephalography appear to be indicated, particularly when the examination is performed for the diagnosis of post-traumatic conditions.

REFERENCES

- 1 Davidoff L M and Dyke C G. *The Normal Encephalogram*. 224 pp. Philadelphia: Lea & Febiger, 1937.
- 2 Lorenz R. Die Bedeutung der Luftabsorption nach Encephalographie für Sitz und Art des interkranialen Prozesses. *Deutsche Zeitsch f Neuroh* 152:230-242, 1941.
- 3 Paul L W and Erickson T C. Observations on presence of subdural gas after pneumoencephalography. *Radiology* 46:139-148, 1946.
- 4 Pendergrass E P and Hodes P J. Encephalography: value of second-day examination. *Radiology* 26:146-150, 1936.
- 5 Schott E and Eitel J. Über die Encephalographie nach Biegel. *Deutsches Arch f klin Med* 141:16-29, 1922.
- 6 Reinberg H. Zur Encephalographiefrage. *Zentralbl f Chir* 52:2057, 1925.
- 7 Friedman E D, Snow W and Kagan J. Experiences with encephalography via lumbar route. *Arch Neurol & Psychiat* 19:762-795, 1928.
- 8 Evans W A Jr. Encephalographic ratio for estimating size of cerebral ventricles: further experiences with serial observations. *Am J Dis Child* 64:820-830, 1942.
- 9 Davies H and Falconer M A. Ventricular changes after closed head injury. *J Neurol & Psychiat* 6:52-68, 1943.
- 10 Torkildsen A and Pirie A H. Interpretation of ventriculograms with special reference to tumors of temporal lobe. *Am J Roentgenol* 32:145-153, 1934.

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Disposition

Combined figures for the disposition of 621 patients with hypertrophic arthritis obtained from ten general hospitals were as follows: to duty, 66 (10.6 per cent), to limited service, 170 (27.4 per cent), and for evacuation, 385 (62.0 per cent). In addition, the probability exists that in many diagnosed as hypertrophic arthritis in station and evacuation hospitals and in the Third Convalescent Hospital the patients were returned to some form of duty without having reached a general hospital.

The disposition in each case was often unpredictable when the patient was first admitted. Cases in which the indications for evacuation were clear from the start included severe cases of the primary type and those with the secondary type in which the underlying cause made improvement under ordinary measures unlikely, as well as patients who had been tried unsuccessfully at limited service and those whose symptoms failed to improve sufficiently with previous hospitalization. It seemed fully justifiable to classify the remainder for limited service with the expectation that, in the majority, the symptoms would be sufficiently controlled to enable the patients to be of use in an assignment in the Zone of Communications not involving undue strain on the involved joints. A small remainder, with mild symptoms responding readily to treatment or with light assignments, were sent to full duty. Finally, the impression was gained that a smaller number of patients were evacuated in the Italian than in the North African phase of operations.

ARTHRALGIA, MYOSITIS AND MYALGIA

This group might be called the "unwanted stepchild" of the arthritic diseases as seen in the Theater. The patients presented complaints without objective findings, were often suspected of neurosis or malingering and furnished real difficulty in diagnosis, treatment and disposition. But, since the cases made up the largest proportion with com-

plaints referable to the joints and other supporting structures, the condition had to be dealt with if not always to the satisfaction of the medical officer's scientific principles, at least in a practical manner. In the collection of data, even more than the usual confusion associated with the nomenclature of the arthritic diseases was encountered. The most frequent term employed in the diagnosis of patients with pain and stiffness of the joints without evidence of a real arthritis or an underlying neurosis was "arthralgia." Myositis or myalgia was employed

TABLE 2 *Classification of the Underlying Causes of Secondary Hypertrophic Arthritis in 100 Patients*

CAUSE	NO OF CASES
Structural abnormalities	
Spinal disease	11
Osteochondritis	5
Congenital defect fifth lumbar vertebra	4
Scoliosis	1
Spondylolisthesis	1
Hip disease	10
Legg-Perthes disease	4
Slipped epiphysis	1
Congenital dislocation	1
Coxa vara	1
Os acetabuli	1
Obesity	5
Cenu varum	1
Previous trauma	74
Old joint injury	35
Knee	15
Spine	10
Elbow	3
Shoulder	2
Ankle	1
Hip	1
Metatarsophalangeal	1
Acromioclavicular	1
Old fracture	41
Spine	8
Ankle	5
Femur	4
Wrist	4
Elbow	2
Knee	2
Humerus	2
Tarsus	2
Patella	1
Hip	1
Pelvis	1
Acetabulum	1
Previous arthritis	1
Infectious hip	1

when the symptoms were localized to the region of muscles rather than joints and when the process was relatively acute. A few hospitals used "fibrositis" or the variation "fibromyositis," according to British usage, which is followed by some in the United States under the assumption that a definite pathologic process is responsible — namely, inflammation of white fibrous tissue. Since this assumption has never been adequately proved, it seemed preferable to discard the term "fibrositis" for the present purpose. Furthermore, since a definite myositis is as incapable of proof as fibrositis in most cases and since, in many cases, the symptoms were in the region of both joints and muscles it was decided to utilize in this section the terms "arthralgia" and "arthralgia group." In this way, unwarranted implications concerning pathology and pathogenesis were avoided, as well as those regard-

had been remissions, either spontaneous or in response to rest or hospitalization. In the secondary type, as might have been expected, the underlying cause was usually operative and productive of some symptoms before entrance on active duty.

In common with civilian experience, objective joint changes were less striking in hypertrophic than in rheumatoid arthritis, acute synovitis or effusion being rare and usually occurring in response to superimposed recent trauma. Findings were limited

diagnosis. In fact, medical officers without exception stated that a definite diagnosis of hypertrophic arthritis was not made in the absence of x-ray changes. As pointed out below under arthralgia, however, the presence of an early hypertrophic arthritis without x-ray changes may have been surmised but not diagnosed in certain patients on account of their age and the localization of symptoms.

Since the diagnosis of hypertrophic arthritis depended almost entirely on positive x-ray findings,

TABLE 1 Age Distribution of Patients* with Various Types of Arthritis, as Obtained from the Records of the Tenth General Hospital

AGE	PRIMARY HYPERTROPHIC ARTHRITIS		SECONDARY HYPERTROPHIC ARTHRITIS		ARTHRALGIA		PSYCHOGENIC RHEUMATISM	
	NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE
15-19	0	0.0	0	0.0	1	1.2	2	3.9
20-24	0	0.0	2	11.8	2	2.3	9	17.6
25-29	1	3.2	2	11.8	15	17.4	15	29.4
30-34	4	11.6	8	47.0	17	19.7	17	33.4
35-39	5	14.7	4	23.5	26	30.4	7	13.7
40-44	11	32.2	0	0.0	17	19.7	1	2.0
45-49	11	32.2	0	0.0	7	8.1	0	0.0
50-54	2	5.9	1	5.9	1	1.2	0	0.0
Totals	34		17		86		51	

*The mean age was 41.7 years among patients with primary and 33.3 years among those with secondary hypertrophic arthritis, 34.1 years among those with arthralgia and 29.2 years among those with psychogenic rheumatism.

largely to crepitus, tenderness, bony irregularity and slight degrees of limitation of motion. The distribution of the arthritis was of some assistance in diagnosis and corresponded to that noted in civilian life. In the 33 patients with the primary type listed in Table 1, the upper extremities, including the shoulders, fingers and acromioclavicular joints, were rarely the seat of symptoms. Heberden's nodes, except for the form secondary to athletic or occupational trauma, were seldom noted in soldiers in the Theater. The spine was oftenest involved, chiefly in the lumbar region, although radicular pain associated with hypertrophic arthritis of the cervical spine was occasionally recorded. Next to the spine, joints of the lower extremities were most frequently affected, especially the hips and knees. In one hospital, a number of patients with hypertrophic changes in the tarsal joints had been admitted with a diagnosis of foot strain.

In the primary type of hypertrophic arthritis, bilateral involvement of corresponding joints was present in a fair number of cases, but a symmetrical distribution was nowhere near so striking as in rheumatoid arthritis. Bilateral arthritis was unusual in the secondary form, in which there was a wider distribution of articular involvement (Table 2) and in which the spine, knees and hips were generally involved.

Laboratory tests were of little assistance in the diagnosis of either type of hypertrophic arthritis. The sedimentation rate was usually normal. Roentgenograms, on the other hand, were essential in the

there is little need of discussing the differential diagnosis. The danger of assuming that the patient's symptoms were necessarily associated with these findings was apparent, however, especially in dealing with radicular pain, in which the ruling out of other possible causes was rightly considered a prerequisite to a final diagnosis of hypertrophic arthritis alone. In a certain number of cases the symptoms were chiefly or entirely dependent on neurosis rather than the arthritis demonstrated by x-ray examination. The finding of mild degrees of hypertrophic arthritis in older soldiers, who may have had skeletal symptoms but whose chief trouble was a lack of sufficient stamina for combat duty, led to the use of this diagnosis as a convenient method of assigning the patients to limited service. Among 132 patients sent to limited service with a diagnosis of arthritis by the Third Convalescent Hospital, a report states that 20 should more properly have been designated "over age for combat service."

Treatment and Course

Since articular cartilage is a tissue displaying little capacity for repair, the changes in hypertrophic arthritis are irreversible, and the condition is usually slowly progressive. No specific medical treatment is available, and surgery to correct causative or accelerating factors was rarely indicated in an overseas theater. The measures employed were therefore chiefly symptomatic and consisted largely in rest and freedom from weight bearing, as well as in the application of heat. Certain cases were bene-

ted by orthopedic measures, chiefly exercises to improve bodily mechanics and strengthen supporting muscles with the occasional use of foot plates or supports for the lower back. Except in severe cases, trial of such methods seemed justified with a view to returning the patient to some form of duty, usually at a lower level of physical activity than in his previous assignment. In planning the extent of the treatment and hospitalization, it was of assistance to realize that the disease is prone to partial or even nearly complete symptomatic remissions both spontaneous and in response to the removal of environmental or occupational factors causing excessive strain on the affected joints. Each case was necessarily handled individually, with the knowledge that the severity of the arthritis, as evidenced by the x-ray film, did not necessarily foretell the outcome.

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Slipped epiphysis	1
Congenital dislocation	1
Coxa vara	1
Of acetabuli	1
Obesity	1
Genu varum	1
Previous trauma	74
Old joint injury	1
Knee	10
Spine	2
Elbow	2
Shoulder	1
Ankle	1
Hip	1
Metatarsophalangeal	1
Acromioclavicular	1
Old fracture	41
Spine	8
Ankle	5
Femur	4
Wrist	4
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Coxa vara	1
Os acetabuli	1
Obesity	1
Genu varum	1
Previous trauma	74
Old joint injury	1
Knee	10
Spine	2
Elbow	2
Shoulder	1
Ankle	1
Hip	1
Metatarsophalangeal	1
Acromioclavicular	1
Old fracture	41
Spine	8
Ankle	4
Femur	4
Wrist	4
Elbow	7
Knee	2
Humerus	2
Tarsus	2
Patella	1
Hip	1
Pelvis	1
Acetabulum	1
Previous arthritis	1
Infectious hip	1

when the symptoms were localized to the region of muscles rather than joints and when the process was relatively acute. A few hospitals used "fibrositis" or the variation "fibromyositis," according to British usage, which is followed by some in the United States under the assumption that a definite pathologic process is responsible — namely, inflammation of white fibrous tissue. Since this assumption has never been adequately proved, it seemed preferable to discard the term "fibrositis" for the present purpose. Furthermore, since a definite myositis is as incapable of proof as fibrositis in most cases and since, in many cases the symptoms were in the region of both joints and muscles it was decided to utilize in this section the terms "arthralgia" and "arthralgia group." In this way, unwarranted implications concerning pathology and pathogenesis were avoided, as well as those regard-

ing the presence of a chronic or progressive disease. The objections noted above apply also to the use of the diagnosis "chronic arthritis, type undetermined," as employed in some hospital records. Since no attempt was made to cover the subject of organic or functional disorders of the lower back, unless caused by some form of arthritis, patients with pain and stiffness confined to this region were not included under the heading of arthralgia. More definite and localized affections are also not considered, such as strains, sprains, bursitis and tenosynovitis.

Incidence

No exact figure can be given for the incidence of arthralgia in the Theater. A total of 918 cases were reported by questionnaire from ten general hospitals, 497 being labeled arthralgia and 421 myositis or myalgia. This figure probably needs little correction for duplication of cases and, in fact, should be higher, with the addition of patients from the group with the diagnosis of chronic arthritis, type unspecified. The patients with arthralgia probably made up nearly 40 per cent of the total number with arthritis admitted to general hospitals, as compared with about 25 per cent each for rheumatoid and hypertrophic arthritis and 10 per cent or less for specific infectious arthritis. The incidence of arthralgia was probably higher in lower medical echelons in the Theater, since many patients were undoubtedly discharged to duty without having been admitted to a general hospital. Patients without objective findings of joint disease were reported to make up the majority of those admitted with articular complaints to one evacuation hospital, whereas they comprised at least half of those listed under arthritis in the records of the Seventy-third Station Hospital. Other available figures in World War II include an incidence of 70 per cent for "fibrositis" among the patients with arthritis admitted to two British general hospitals in 1940,³ contrasted with 5 per cent in a general hospital in the United States² and 13.6 per cent at the Army and Navy General Hospital, Hot Springs, Arkansas.⁴ The smallness of the last percentages may have been due to the fact that in the American hospitals a special search was made for cases of psychogenic rheumatism among the patients without evidence of real arthritis. In World War I, in about 25 per cent of the 65,192 patients admitted to Army hospitals for arthritis the diagnosis was muscular rheumatism or myositis.⁵

Etiology

A sample to show the age distribution of patients with arthralgia was obtained from a series of 86 patients in the records of the Medical Service of the Twelfth General Hospital (Table 1). Patients were selected, irrespective of the hospital diagnoses, who complained of pain and stiffness in and around the joints without clinical, laboratory or x-ray evidence

of arthritis. This group tended to be made up of older patients, the mean age (thirty-four years and one month) being higher than that in rheumatoid arthritis (thirty years and nine months), but considerably lower than that in hypertrophic arthritis (forty-one years and eight months). This finding, although noted in other hospitals, may be only apparent, since a frequent practice in the Theater was to return young patients with arthralgia to duty, whereas older soldiers were likelier to be sent to a general hospital to be classified for limited service. No clue was obtained in the Theater regarding the actual causes of arthralgia, but precipitating factors included severe exertion and exposure to cold and dampness. An increase in the number of cases from the Fifth Army hospitals was noted at the Third Convalescent Hospital at the beginning of the cold and rainy season. There were few cases of acute infections of the upper respiratory or gastrointestinal tract directly preceding the onset of symptoms, although such conditions were often accompanied by transitory skeletal aches and pains.

Diagnosis and Clinical Features

In the diagnosis of arthralgia, a careful history was all important. Unless the patient's symptoms were characteristically "rheumatic," a strong suspicion of psychogenic rheumatism properly arose. The necessary points for a rheumatic symptomatology may be listed as follows: morning stiffness and an increase in pain after sitting or lying in one position during the day, aggravation by cold, dampness or weather changes, and at least temporary relief from heat, moderate exercises and aspirin. Severe exertion, with overuse of the joints and muscles during the day, may, of course, cause an increase in pain or stiffness toward evening as well as on arising. It was found necessary for the examiner to avoid the use of leading questions and to realize that a soldier may have had an opportunity to compare notes with a fellow sufferer from arthritis, especially on a hospital ward. Marked constitutional or vasomotor symptoms were unusual in this group and, when present, suggested the possibility of a mild rheumatoid arthritis. The same observation held true of neurologic symptoms, with motor weakness and tremor again suggesting rheumatoid arthritis. Bizarre paresthesias or numbness in contrast to genuine pain and stiffness were often indicative of a psychogenic origin of symptoms.

The physical examination in these patients showed no objective changes in the form of swelling or joint effusion, although the patient might complain that his joints felt swollen. Mild or moderate degrees of limitation of motion, which were occasionally present, were associated with muscle spasm or stiffness rather than actual loss of joint function. Tenderness over joints, muscles and other supporting structures and pain on motion of joints or on stretching of muscles were frequently elicited. The

distribution of involvement is presented in Table 3. As indicated by the figures, many patients had involvement of multiple regions, the lower extremities being affected about twice as often as either the back or the upper extremities.

The sedimentation rate was uniformly normal in patients with arthralgia. The one exception consisted in a few patients with marked tenderness chiefly localized to the lumbar paravertebral muscles, in all of whom the sedimentation rate was moderately elevated, and in some cases there was a suggestion of muscle swelling, along with fever and leukocytosis. The course was that of slow improvement, with a disappearance of symptoms and signs and a return to normal of laboratory findings. Despite careful observation over a relatively long period, they never developed evidence of disease of bones or joints and were eventually returned to duty. In such patients alone, a diagnosis of myositis seemed justified. X-ray examination of the involved region was performed in nearly all hospitalized patients with arthralgia, with negative results.

Differential Diagnosis

A final diagnosis of arthralgia in a patient with the findings described above depended on the exclusion of either a real arthritis or an underlying neurosis as a cause for symptoms. Much difficulty arose in the elimination of an early, mild rheumatoid arthritis, since the articular distribution including symmetry often suggested this disease. The differentiation of hypertrophic arthritis depended almost entirely on the x-ray findings. In many patients, on account of the age distribution (Table 1) and the localization of symptoms to the back and lower extremities (Table 3), the question of an early hypertrophic arthritis without x-ray changes was properly raised. In such cases the practice was to employ arthralgia as an immediate diagnosis, with the reservation that hypertrophic arthritis might be revealed by x-ray study at a later date. A careful orthopedic check-up examination proved useful in a number of patients by revealing structural abnormalities that might previously have been overlooked. These included foot strain, genu valgum, varum or recurvatum, bursitis in various localities and organic changes of the spine. Rheumatic fever was rarely difficult to distinguish, but electrocardiographic study of an occasional case showed a definite increase in the PR interval and favored a presumptive diagnosis of this disease.

Most important of all to eliminate in the arthralgia group was a neurotic basis for symptoms, or so-called "psychogenic rheumatism." The distinction was made on two grounds: the demonstration of an underlying neurosis, with psychiatric aid in certain cases, and the finding, after careful evaluation, that the patient's symptoms were not characteristically "rheumatic," as described above. In certain patients, in whom both neurosis and arthralgia were

apparently present, careful clinical judgment was required to ascertain the predominant factor, the use of two diagnoses occasionally being justified. The medical officer was helped in this decision by the age of the patient (the symptoms seemed genuine more frequently in older patients) and, if available, by the opinion of the soldier's commanding officer. It seemed probable, however, that many cases of neurosis had inaccurately been labeled arthralgia or a similar diagnosis. The much larger number of patients found in a general hospital in the United States with psychogenic rheumatism than fibrositis has been mentioned above,² whereas in civilian prac-

TABLE 3 Areas of Body Affected by Arthralgia among 86 Patients, as Obtained from the Records of the Twelfth General Hospital

AREA	No. of Cases
Upper extremities	62 (51%)
Shoulders	22
Elbows	10
Hands	8
Wrists	11
Back	49 (24%)
Cervicodorsal	15
Lumbosacral	34
Lower extremities	90 (45%)
Knees	46
Hips	19
Legs	12
Ankles	11
Feet	2

tice in England, Halliday⁶ considered the disability due to psychogenic factors in 37 per cent of 62 insured patients with a diagnosis of rheumatism. The question of malingering occasionally arose in these patients but seemed incapable of proof. Conscious or unconscious exaggeration of symptoms was not unusual, however, and was generally readily recognized and appropriately handled by the medical officer.

Treatment and Course

The treatment of the patients with arthralgia was usually symptomatic and included the benefits of hospital shelter and care (rest, warmth, sleeping off the ground and avoidance of severe exertion), relief of pain with salicylates and physical therapy in the form of heat, massage and exercises. Some success was attained in the more acute, localized types, but the generalized forms seemed to derive only temporary, if any, alleviation of symptoms. In the latter, prolonged hospitalization proved ineffective and indeed wasteful of bed space and manpower once the diagnosis had been established. A decision regarding diagnosis and disposition was therefore indicated as quickly as possible. Along these lines, greater stress should have been laid on handling the problem more frequently in the Army area or in station hospitals in the Zone of Communications. In this way, with a relatively short period of observation, a sorting could have been made of cases

that were obviously functional, those with arthralgia and those with probably real arthritis. Fewer patients in the first two groups would then have needed to be sent to general hospitals.

Disposition

Figures from ten general hospitals showed the following proportion of dispositions for 918 patients with arthralgia to duty, 538 (58.6 per cent), to limited service, 263 (28.6 per cent), and for evacuation, 117 (13.8 per cent). The percentage of patients with myalgia or myositis who were evacuated was essentially the same as that in cases of arthralgia, but a greater proportion of the former were returned to full duty. It was the opinion of medical officers questioned in evacuation and station and most general hospitals that a large majority of the patients with arthralgia were sent to duty. The exceptions comprised patients who had repeatedly failed at full duty, older soldiers who were otherwise unsuited for combat and those whose commanding officers believed that they should be reclassified. The small number evacuated were mainly soldiers who were unable to perform even limited service or those with a severe psychoneurosis in addition. The remainder were sent to limited service and were usually able to carry on without rehospitalization. In summary, from the general hospital figures, nearly 90 per cent of patients with arthralgia were returned to some form of duty, with the probability that an even larger proportion from evacuation and station hospitals were sent to full duty, rather than to limited service.

PSYCHOGENIC RHEUMATISM

The term "psychogenic rheumatism" was adapted from the work of Boland and Corr² at the Hoff General Hospital, Santa Barbara, California. Their definition of this condition is as follows: "states in which symptoms such as pain, stiffness, subjective sense of swelling or limitation of motion in the muscles or joints are caused, intensified or perpetuated by mental influences." A similar name, "psychosomatic rheumatism," was used in England for a number of years by Halliday,⁷ who stressed the high incidence of this cause of articular symptoms, especially in cases labeled fibrositis. Although psychogenic rheumatism is a convenient and concise descriptive term for this group of patients, it should be made clear that it is not advocated as a final diagnosis in the records of Army or civilian hospitals. The usual diagnoses of neurosis or psychoneurosis, with the type and manifestations, should be employed.

Incidence

About one sixth (16.5 per cent) of 309 patients with articular complaints admitted to the Medical Service of the Twelfth General Hospital were believed to be suffering from psychogenic rheumatism.

This proportion, which was equaled by that of patients with hypertrophic arthritis and was exceeded by patients with arthralgia (33.4 per cent) and rheumatoid arthritis (24.8 per cent), outnumbered the remainder, chiefly patients with specific infectious arthritis (8.0 per cent). At the Army and Navy General Hospital, in 18.8 per cent of patients with rheumatic complaints the diagnosis was psychogenic rheumatism,⁴ a somewhat greater proportion—60 (26 per cent) of 231 patients with peripheral joint involvement—being so classified by Boland and Corr,² who were especially interested in and on the lookout for this condition. These authors, in fact, found psychogenic rheumatism the most frequent cause of disability encountered in their series, although the incidence was only slightly in excess of that of rheumatoid arthritis.

Another method of approach to the incidence of psychogenic rheumatism was an estimate of the proportion of cases of neurosis manifested by symptoms referred to the joints, muscles or other supporting structures. In a study of patients admitted to the Fifty-sixth Evacuation Hospital with diagnoses of organic diseases, 174 patients whose symptoms were actually on a functional basis were recorded and classified. The diagnosis of some form of arthritis on admission was made in only 13 (7.5 per cent), as compared with 51 patients, or 29 per cent, admitted with gastrointestinal disease, 25 patients, or 14 per cent, with upper respiratory symptoms, 19 patients, or 11 per cent, with backache and 14 patients, or 8 per cent, with headache. These figures were also confirmed by neuropsychiatric opinion, which put articular manifestations of the neuroses at the end of a list including, in order of frequency, backache, gastrointestinal symptoms, headache and cardiovascular symptoms. At the Six Hundred and First Clearing Company, where patients with neuroses were gathered directly from the Fifth Army and were nearly all considered "battle incurred," this symptom-complex was rarely encountered. Most of the patients manifested "free anxiety," and it was believed that somatic symptoms in this group usually developed after hospitalization. Major hysteria, however, in the form of gaits, postures and joint symptoms that might mimic a real arthritis, made up perhaps 2 or 3 per cent of the admissions. A few such patients were also seen in hospitals in the Zone of Communications, only 10 being listed in the questionnaires. The experience of Boland and Corr² in the United States is at variance with the information available for the Mediterranean Theater. These authors stated that disabling psychogenic complaints, as observed in an Army general hospital, were displayed frequently in the joints and muscles and were comparable to their occurrence in the gastrointestinal and cardiovascular systems. The difference may lie in the as-siduity with which they searched for this type of

case and in the fact that they included patients with low-back symptoms on a functional basis

Etiology

The immediate precipitating emotional cause, as Boland and Corr² have pointed out, was difficult to elicit and was not often found in the records. Factors common to the development of other manifestations of neurosis in troops overseas were undoubtedly active and need not be listed here. In general, the patients seemed younger than those with an actual arthritis and, as one medical officer put it, "can be picked out of the younger patients with arthralgia." Table 1 shows the age distribution in 51 patients from the records of the Twelfth General Hospital. A comparison with other types of arthritis in this table reveals that patients with psychogenic rheumatism approximately equaled in age those with rheumatoid arthritis, but comprised a definitely younger group than those with hypertrophic arthritis or arthralgia. In Boland and Corr's² series, on the contrary, no relation to age was found.

Except in the experience of the Six Hundred and First Clearing Company, precipitation or aggravation by combat was frequent, about half the patients admitted to the Twelfth General Hospital having given this history. A distinction was not always made in the record, however, between the onset of the anxiety state and the actual somatic fixation. In common with the findings of Boland and Corr,² about half the patients presented a history of articular symptoms. In many of these cases there was an actual history of injury to a joint or a preceding disease accompanied by pains in the joints, such as rheumatic fever, influenza or meningitis (stiff neck), but without objective changes on examination. In most cases it was impossible to determine from the record whether the patient had had psychogenic rheumatism in the past or whether the previous injury or disease had merely provided a site for somatic fixation of the neurosis. A family history of "rheumatism," found in over a third of the patients studied in the United States, was not prominent in the Theater, except for a few striking cases, but might have been brought to light oftener by direct questioning. The presence of an underlying neurosis, dating back to civilian life in over half the cases, evidently furnished the cause for the development of somatic symptoms. This was brought out by past and family histories of neuropathy and by the elicitation of other psychosomatic symptoms, some on a frankly hysterical basis. About half the patients at the Twelfth General Hospital gave evidence of general or localized functional symptoms in addition to those directed toward the joints. The role of hospitalization in the development of somatic symptoms, as postulated by the Six Hundred and First Clearing Company, was difficult to demonstrate with numerical data, but most medical officers questioned could recall specific cases, occasionally

with direct contagion from fellow patients with joint complaints

Diagnosis and Clinical Features

The diagnosis of psychogenic rheumatism depended on two criteria. The first was the ruling out of organic disease as the important factor in the patient's complaints, with the aid of the principles outlined in the sections on individual types of arthritis and, in doubtful cases, with the help of a careful orthopedic examination. The second consisted in the establishment of a positive diagnosis of neurosis, by a family or past history of neuropathy and by the presence of other psychosomatic symptoms. Persistence or return of symptoms localized to the site of previous disease or injury was useful in arousing suspicion, as well as a family history of joint disease with symptoms similar to those of the patient. Bizarre complaints, including paresthesias and numbness and symptoms not typically "rheumatic" (as outlined above), served to direct the examiner's attention to functional disease. In certain patients the opinion of a psychiatrist was of great value, either in confirmation of the internist's opinion or to bring out the patient's neurotic background by a trained psychiatric approach.

The physical examination in these patients was usually entirely negative. A certain number presented joint limitation or deformity associated with muscle spasm. Others showed mild residual changes that were obviously not responsible for the symptoms. In a third group, areas of hysterical anesthesia were present, either in a glove and stocking distribution or in the neighborhood of the involved joints. Patients with hysterical gaits and postures, including camptocormia, and with joint deformity without actual arthritis were usually easily identified, sometimes with the aid of sodium amytal narcosis. The distribution of articular involvement corresponded to that found by Boland and Corr,² the majority complaining of symptoms in the back and lower extremities, compared with a smaller number of cases with symptoms in the upper extremities or generalized.

The psychiatric diagnosis made in the 51 patients from the Twelfth General Hospital was variable, without the majority showing an anxiety state as found in the series in the United States.² A classification of the types of psychoneurosis is as follows: conversion symptoms or hysteria, 18; anxiety state, 18; hypochondriasis, 7; unclassified or mixed, 4; and constitutional psychopathic state, 4.

In the differential diagnosis organic types of joint disease, including arthralgia and orthopedic conditions, were chiefly considered. Rheumatoid arthritis furnished some difficulty even after a careful examination and an adequate period of observation. Several patients were seen, however, who had been admitted with a diagnosis of neurosis and whose symptoms were found to be entirely explain-

able on the basis of rheumatoid arthritis with marked constitutional manifestations. In a larger number — 10 of 132 patients at the Sixth General Hospital with rheumatoid arthritis — two diagnoses were properly made, with the coincident neurosis usually of the anxiety type. In some cases the arthritis apparently became worse after the development of the neurosis, but in at least one soldier who had carried on in spite of a well marked arthritis, the anxiety was obviously secondary to the disability and to a feeling of helplessness in the presence of danger. Since the diagnosis of hypertrophic arthritis was made largely by means of x-ray examination in the Theater, patients chiefly required mention whose symptoms were out of all proportion to the organic findings. Such patients, if there was positive evidence of neurosis, were usually given two diagnoses, one of which included "psychoneurosis, manifested by elaboration of a minor organic illness." Others, who showed hypertrophic changes only incidentally or with presenting symptoms entirely unrelated, were also given two diagnoses, with the lack of importance of the arthritis clearly indicated. Points found useful in the distinction between arthralgia and psychogenic rheumatism have been outlined above. As a final check, even in apparently clear-cut cases of neurosis, it was well to have an orthopedic examination to eliminate structural changes of the skeletal system as a partial or complete cause of the patient's disability.

Treatment and Course

The treatment of psychogenic rheumatism was largely unsuccessful once the patient reached a general hospital, whether the symptoms were long present, were precipitated by combat or the hardships of military life or became localized and fixed during previous hospitalization. About all that was accomplished was to reassure the patient (and the medical officer) that no serious form of arthritis was present and to determine the disposition according to the patient's degree of disability. An even more pessimistic conclusion was reached by Boland and Corr,² who found that their efforts to return such patients to full or limited duty were largely unsuccessful. Their group, however, was made up of men undergoing training in the United States, and in many cases the only solution was the removal of the underlying mental conflict, which could be accomplished by separation from military service. The authors stress the need for prompt recognition and proper psychotherapy instead of physical therapy, a point that was equally applicable, as mentioned above, to the Theater. For example, it was found possible at the Six Hundred and First Clearing Company to send most of the patients with hysterical manifestations localized to the skeletal system at least to limited service by early applica-

tion of treatment before the symptoms became intensified and fixed. The methods consisted in the clearing up of symptoms with the aid of barbiturate narcosis and suggestion. The patients were usually told in addition that their combat days were over but that prolonged and unpleasant hospitalization was in store for them unless they became well enough for limited service.

Disposition

In the series of 51 patients with psychogenic rheumatism from the Twelfth General Hospital only 4 (8 per cent) were returned to duty, 30 (60 per cent) were sent to limited service and 17 (32 per cent) were evacuated. Although it was agreed that disposition by general hospitals should be individualized according to the degree of neurosis and an estimate of the patient's ability to perform useful service, the impression was gained that the majority were discharged to limited service. A few, especially those with mild or exaggerated symptoms, were sent to full duty, such a disposition being more probable in forward medical echelons. The remainder, usually with a severe underlying neurosis and a deep fixation of symptoms, were evacuated.

SUMMARY

Hypertrophic arthritis was encountered in the Mediterranean Theater as frequently as rheumatoid arthritis, a finding associated with the presence of older officers and soldiers and a high incidence of the secondary type. Symptoms usually existed prior to induction, the hardships and physical strain of military service being precipitating factors in hospitalization. Previous joint trauma or fractures were responsible for the development of the secondary type about three times as often as structural abnormalities. The diagnosis of hypertrophic arthritis was established by x-ray examination, with care necessarily taken to ascertain the relation of the x-ray findings to the patient's disability. The proportion of patients sent to limited service was greater than that in patients with rheumatoid arthritis.

Reasons are advanced for the use of the term "arthralgia" in patients with symptoms referred to the joints, muscles and other supporting structures, without evidence of a true arthritis or a causative neurosis. The high incidence of cases of arthralgia is stressed. Symptomatic treatment was effective only in the acute and localized forms, in which the diagnosis of myositis or myalgia was often made. Over 50 per cent of these patients were returned to full duty, and another 25 per cent to limited service.

At least a sixth of the patients with articular complaints were found to have a neurotic basis for their symptoms — so-called "psychogenic rheuma-

tism" Articular localization of psychosomatic manifestations was less frequent than backache, headache and gastrointestinal or cardiovascular symptoms. Precipitation or aggravation of the neurosis by combat was frequent, and many patients gave a history of previous joint disease or injury. About half the patients had additional generalized or localized functional symptoms. Treatment was ineffective except in patients seen soon after the onset of symptoms in a forward area.

CLINICAL NOTE

MONGOLISM FOLLOWING INTERCURRENT INFECTIOUS DISEASE IN PREGNANCY*

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IT IS generally agreed that mongolism is not hereditary in the sense that hemophilia and color blindness are hereditary.^{1,2} Abundant evidence⁴ shows that the risk of mongolism is greater in mothers of advanced age than in those who are younger. There is also a higher frequency of mongolism in homozygote as contrasted with heterozygote twins.³ By some this is interpreted to mean that the ovum or sperm is defective. Early reports tending to implicate diseases like syphilis, tuberculosis, malaria and alcoholism² are inadequate to explain the large majority of cases. Indeed, no one etiology has been shown for the condition.

No cases have been reported that correlate minor maternal illnesses with the subsequent development of the condition. The recent discovery that maternal rubella may be followed by such widely disseminated and such severe fetal consequences as congenital cataract, anomalies of the heart, microcephaly and mental retardation^{4,5} has brought about a sudden change of perspective to both pediatricians and obstetricians. This change has to do with their point of view toward maternal infections that were once considered too trivial in their effect on the mother to have any bearing on fetal health. With this changed opinion in mind, we report 7 cases of intercurrent infectious disease observed during pregnancies that terminated in the delivery of a mongoloid baby. These are listed

REFERENCES

1. Short, C. L. Arthritis in Mediterranean Theater of Operations. I. Incidence of joint disease—clinical description of rheumatoid arthritis. *Ver. Ent. J. Med.* 236: 38-39, 1947.
2. Boland, E. W. and Corr, W. P. Psychogenic rheumatism. *J. A. M. A.* 123: 805-807, 1947.
3. Hench, P. S., Osgood, R. B. and Wainwright, C. W. Outline of diagnosis and treatment of common rheumatic diseases. *Arch. Int. Med.* 60: 127, 1942.
4. Bauer, W. Personal communication.
5. U. S. War Department Surgeon General's Office. *The Medical Department of the United States Army in the World War*, 17 vol. Washington: Government Printing Office, 1921-1929.
6. Halliday, J. L. Psychological factors in rheumatism: preliminary study. *Brit. M. J.* 1: 21, 217 and 264-269, 1947.
7. Loefer, J. Concept of psychosomatic rheumatism. *Arch. Int. Med.* 15: 666-677, 1941.

in Table 1. The localization of the particular disease in 6 of the 7 cases at about the end of the second month of pregnancy is provocative. It is more so in view of the long recognized association of mongolism with such congenital deformities as cleft palate, syndactyly and imperforate anus, which date from about the same period of fetal life.⁶ We believe that further epidemiologic studies are indicated to show whether acute maternal infections correlate with the subsequent development of mongolism.

Even if acute intercurrent infectious disease proves to be one factor in the etiology of mongolism, it probably accounts for only a small fraction of all cases. The problem of demonstrating such a factor is not dissimilar to that posed by the relation of tonsillectomy to subsequent poliomyelitis, tonsillectomy being shown to be a factor in a small fraction

TABLE 1 Data on Mothers of Mongoloid Babies Who Had Intercurrent Diseases during Pregnancy

AGE OF MOTHER	INTERCURRENT DISEASE	STAGE OF PREGNANCY
37		11*
25	Influenza	2
34	Rubella	2
29*	Mumps	2
47(†)†	Mastoidectomy	2
9	Pneumonia (in bed 2 wk.)	3
52	Grippe	6
27‡	Acute purulent otitis media and sinusitis (with vomiting)	2

*The information on this case was furnished by Dr. Richard C. Teet.
†Mother had pneumonia at birth of child and died.
‡On a diet during first month of pregnancy patient lost 15 pounds.
§Sinusitis occurred just prior to otitis. Mother was admitted to hospital because of vomiting necessitating intravenous administration of fluids.

of all cases (about 1 per cent). The relation was demonstrated not by the ratio of cases of poliomyelitis to tonsillectomies but by a significant pyramiding of the developing cases, ten to twenty days postoperatively.⁷

In determining the relation of intercurrent infectious disease to mongolism, the week of pregnancy in which the particular disease occurred is of statistical importance. Since there are forty weeks to a normal pregnancy, there is only one chance in forty for a given illness to occur in any particular week—if the phenomenon is a chance one. When a sufficient number of cases are assembled, the figures can be submitted to statistical analysis.

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We hope that this brief communication will prompt physicians to provide us with further data

REFERENCES

- 1 Benda, C E. *Mongolism and Cretinism. The interaction of endocrine glands* 350 pp New York Grune & Stratton 1946
- 2 Brousseau, K, and Brainerd, H G. *Mongolism. A study of the physical and mental characteristics of mongolian imbeciles* 210 pp Baltimore Williams & Wilkins 1928
- 3 Ford, N, and Frumkin, S. Monozygosity in mongoloid twins. *Am J Dis Child* 63 847 858 1942
- 4 Gregg N M. Rubella during pregnancy of mother with a sequelae of congenital defects in child. *N J Australia* 1 313 315 1945
- 5 Swan, C, Tostevin, A L, Mayo H, and Black, G H B. Further observations on congenital defects in infants following infectious diseases during pregnancy with especial reference to rubella. *N J Australia* 1 409-413, 1944
- 6 Weatherford H L. Personal communication
- 7 Aycock, W L. Tonsillectomy and poliomyelitis epidemiologic considerations. *Medicine* 21 63 94 1942
- 8 Eley, R C, and Flake, C G. Acute anterior poliomyelitis following tonsillectomy and adenoidectomy with special reference to bulbar form. *J Pediat* 13 63 70 1938

MEDICAL PROGRESS

PATHOLOGY*

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FOUR years have elapsed since I have had the privilege of recording progress in pathology for this series. During that period staffs of civilian laboratories were cut to the bone, and the demands of routine diagnostic work and year-round teaching under the accelerated program of medical education left little opportunity or energy for investigative work. To a considerable extent this was balanced by the necessity of pathological investigation of problems of military importance, a need largely cared for in this country by the farsighted policy of the United States Army in developing and progressively expanding the Army Institute of Pathology with its large corps of full-time workers and its part-time consultants. The unparalleled collection of anatomic material that has flowed into it from every corner of the globe has already permitted many studies of importance. A portion has already been published, publication of much more is imminent and study of the remaining material will occupy as large a corps of investigators as can be maintained for years to come.

Any attempt to survey the entire field of pathology for a four-year period would require such cursory treatment as to be completely valueless. A few features only have been selected because they seem to be of more than casual interest and importance.

Rheumatic Fever and Periarteritis Nodosa

One of the most interesting conceptions in pathology in recent years is the hypothesis advanced by Rich¹ that the lesions of periarteritis nodosa and rheumatic fever are the result of anaphylactic hypersensitivity. The possibility that rheumatic fever is a hypersensitive reaction had been entertained for many years by a variety of investigators, and the early literature was reviewed by Swift² and Gross,³

in 1929, and again by Coburn⁴ in 1931. Gross repeated many of the reported experiments with negative results. In succeeding years Klinge,⁵ Vaubel⁶ and Junghans⁷ each claimed to have produced lesions of the rheumatic type by sensitization of animals with horse serum, but their published illustrations were not convincing. Bruun,⁸ in 1940, repeated their experiments with only equivocal results and concluded that he had not reproduced a true analogue of the Aschoff nodule.

In 1942 Rich⁹ reported autopsies on 5 patients who had had serum sickness shortly before death, in all of whom vascular lesions characteristic of periarteritis nodosa were demonstrable. None of the patients had any symptoms suggestive of periarteritis prior to the acute terminal illness, and all the vascular lesions were fresh. Similar vascular lesions were also demonstrated in 2 patients who had had reactions to sulfonamide therapy.¹⁰ He concluded that vascular lesions of the periarteritic type can be a manifestation of the anaphylactic type of hypersensitivity.

In the following year Rich and Gregory¹¹ reported the experimental production of similar lesions. Rabbits were sensitized with one or more large doses (10 cc) of horse serum. On the fifth to the eighth day the animals developed fever and had a slight blushing of the skin, possibly equivalent to the urticaria of human serum sickness. All animals showed on skin test the immediate, anaphylactic type of hypersensitivity, some developing Arthus reactions with necrosis. They were sacrificed at periods ranging from seventeen to twenty-six days, and the majority showed arteritic lesions characteristic of various stages of periarteritis nodosa.

In an extension of this experiment the same authors¹ found in the hearts of 11 of 36 similarly sensitized rabbits lesions that reproduced closely the five supposedly pathognomonic features of acute rheumatic carditis. These are focal alterations of

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collagen, Aschoff nodules, focal and diffuse inflammatory lesions, focal alterations in cardiac muscle and verrucose valvular vegetations. In the experimental animals connective-tissue alteration was prominent in the endocardium near the valvular attachments, and nodules developed about the foci of damaged collagen composed of large cells with abundant usually basophilic cytoplasm, of which some were multinuclear, and others resembled Anitschkow myocytes. In a few nodules palisading of cells about the altered collagen was observed. These nodular foci were usually formed near the attachments of the valves. Perivascular inflammatory infiltrates were frequent, but nodule formation in the adventitia of arteries — a characteristic location in rheumatic fever — was not observed. Non-specific inflammatory lesions in the endocardium and pericardium were frequent. In 4 animals small foci of necrosis of cardiac muscle fibers were found. No actual vegetations with thrombus formation were noted, although the nodules frequently projected above the surface of the valve to give it a slightly warty appearance. The parallelism traced between the experimental lesions and the histologic findings in acute rheumatic fever is impressive, if not complete, and the excellent illustrations guarantee the objectivity of the verbal descriptions. Evidence for the anaphylactic character of still another rheumatic lesion was furnished by the same authors by a demonstration of the essential similarity of the pulmonary injury following sulfonamide sensitization and that of rheumatic pneumonitis.¹²

The greater success of Rich and Gregory, in comparison with their predecessors, in reproducing histologic features closely simulating those of rheumatic fever in human beings may well have been due to their clear distinction between the anaphylactic and tuberculin types of hypersensitivity and their selection of more appropriate sensitizing regimens. There can be little hesitation over accepting their hypothesis regarding periarteritis nodosa, in which clinical evidence of hypersensitivity, such as eosinophilia or asthmatic paroxysms, is frequently present. Even here, caution is suggested by the reports of periarteritis developing in rats and dogs made hypertensive by clamping of the renal artery¹³ or by wrapping of the kidney in silk.¹⁴ Despite the close parallelism between the symptomatology of rheumatic fever and serum sickness the usual stigmas of allergy are lacking in the former disease, and direct proof of anaphylactic sensitization in rheumatic fever in the human being has yet to be advanced. Studies such as those of Coburn⁴ with streptococcal antigens should be repeated with attention to immediate rather than delayed types of skin reaction.

Acute Disseminated Lupus Erythematosus

Acute disseminated lupus offers so many general features of similarity to and so many details of difference from rheumatic fever that comparison

of the two diseases fascinates clinicians and pathologists alike. A new angle of comparison has been advanced by Klemperer, Pollack and Baehr¹⁵ in a continuation of the pathological studies on lupus that have occupied the laboratory of the Mt. Sinai Hospital for many years. On the basis of a review of the 35 cases that have come to autopsy in that institution, with particular study of the last 20, they have reached the conclusion that the thesis formerly advanced — that lupus is fundamentally a diffuse vascular disease¹⁶ — is no longer tenable. They now present evidence that the basic pathologic lesion is a characteristic type of focal connective-tissue degeneration. All elements take part in the reaction. The mucoid ground substance, ordinarily hardly visible, becomes evident as a swollen homogeneous interfibrillar mass. The collagenous fibers assume a straight, rigid, irregularly thickened appearance and become deeply eosinophilic, assuming the character often designated as fibrinoid. The fibroblasts show degeneration, proliferation and even necrosis. Inflammatory reaction, although variable, is non-specific in type and relatively inconspicuous, and in the authors' words, "the alterative phase of the process is far out of proportion to the exudative." This is in marked contrast to rheumatic fever, a disease in which collagenous degeneration has long been recognized as one of the most important pathologic features, but in which active inflammatory reaction of a specific character about the foci of altered collagen is constant. The involvement of serous cavities is considered secondary to the connective-tissue degeneration of the limiting membranes, rather than to primary mesothelial involvement as Gross¹⁷ suggested. Again, the first change noted in the endocardium and valves was in the connective tissue rather than in the endothelium. The so-called "wire-loop" changes of the glomerular tufts in the kidney are evidently a primary change of the collagen of the capillary basement membranes, and even the focal glomerulitis of other cases can be so interpreted. Vascular lesions, although seen most often in the kidneys, are observed rather frequently in other organs. The mildest recognizable change is a deposit of fibrinoid material within the intima, and later between the muscle fibers of the media and in the adventitia. It is usually accompanied by fibroblastic proliferation. Endothelial damage is definitely considered secondary, in contradiction to previous work from this same laboratory that considered it primary.¹⁸ In severe lesions secondary necrosis of the entire vascular wall may occur, closely simulating the vascular lesions of malignant hypertension or even periarteritis nodosa.

Connective-tissue changes of the type described are much less conspicuous in the skin, although they do occur. It is doubtful if many dermatopathologists would admit that they were primary. In the spleen, fibrinoid degeneration was unusual, but another form of connective-tissue change was found

in 19 of 20 cases. This consists of periarterial fibrosis limited to central and penicillary arteries in the form of concentric rings of dense collagen fibers. This lesion is sufficiently specific to have considerable diagnostic value. Unaccounted for by the theory of primary collagenous injury is the extensive involvement of lymphoid tissue frequently observed.

Rheumatoid Arthritis

Joint lesions so dominate the clinical picture of rheumatoid arthritis that comparatively scant attention has been given to the possibility of involvement of other organs and tissues. The possibility of cardiac involvement has been raised by Baggenstoss and Rosenberg^{18, 19}. Cardiac lesions indistinguishable from ordinary rheumatic carditis were found in several cases of rheumatoid arthritis, and in 2 the histologic picture was similar to that of rheumatoid nodules. Steiner et al.²⁰⁻²² have recently shown that peripheral nerves and muscles are frequently affected. The lesions in both nerves and muscle consist of small aggregates of mononuclear cells, lymphocytes and plasma cells predominating but with occasional macrophages. There is usually no evidence of any core of necrotic collagen as in the rheumatoid nodules, and no palisades of epithelioid cells develop. The foci are found in the perineurium and perimysium of nerves and muscles respectively. Since there is no evidence of axonal or myelin-sheath degeneration, it seems improbable that nerve function is impaired. In the muscles, atrophy was frequently observed, but the evidence for attributing this to the inflammatory foci is not convincing.

In discussion of Steiner's²² paper Clauson reports the results of biopsies of the deltoid muscle from 70 cases of rheumatoid arthritis. In more than half he was able to find lesions similar to those described by Steiner. He also found indistinguishable lesions in a few cases of rheumatic fever.

Atypical Pneumonia

One of the great advantages of a central institute of pathology, such as that fostered by the Army in Washington, is in the study of the pathology of diseases with a low mortality. Few hospital laboratories, for instance, have had the opportunity of studying more than one or two examples of atypical pneumonia. The Army Institute of Pathology has autopsy material from 90 cases in which that diagnosis had been made on clinical grounds. Many were inadequately studied, and others were complicated by secondary bacterial infection, but Golden²³ was able to select 21 entirely acceptable cases for analysis. In this group of cases focal bronchiolitis was a constant finding. The lumens contained frank pus, mucoid secretions and desquamated epithelial cells, sometimes in an advanced stage of disintegration. Ulceration of the mucosa was not rare. Bacteria were absent in most cases,

and when present were neither numerous nor uniform in type. The affected bronchioles were dilated, and their walls were infiltrated with mononuclear cells. This inflammatory infiltrate tended to spread radially into the adjacent tissues, such as the alveolar walls and the interlobular septums. The alveoli were in part aerated, focally atelectatic and occasionally filled with protein-rich edema from which hyaline membranes precipitated on the alveolar walls. They were always relatively free from polymorphonuclear infiltration. Fibrinous pleuritis was unusual, in contrast to its frequency in bacterial pneumonias. In cases of longer duration foci of squamous-cell metaplasia frequently appeared in the bronchi, and the alveoli sometimes became lined with columnar epithelium.

The type of pneumonitis described may fairly be classed as an interstitial pneumonitis. As McCordock and Muckenfuss²⁴ pointed out, viruses that involve the lung tend to produce this type of pneumonitis. Interstitial pneumonitis cannot, however, be considered reliable evidence of virus infection, since it occurs in conditions as different as scrub typhus, Q fever and even histoplasmosis.²⁵

Scrub Typhus

Until the American invasion of the South Pacific, scrub typhus was an unknown disease to most American physicians, and few would even have been able to identify it with the fascinatingly alliterative *tsutsugamushi*, which had lingered as a mere name among the vaguer recollections of medical-school days. From the material of the Army Institute of Pathology, Allen and Spitz²⁶ have been able to describe thoroughly the pathology of the disease and to compare the lesions with those of the related rickettsioses: epidemic typhus, Rocky Mountain spotted fever and Q fever.

A noticeable primary lesion, known as the eschar, usually develops at the point of the mite bite. This is often frankly suppurative and probably represents a combined reaction to the inoculated rickettsias and to the irritating secretions of the mite. In contrast to epidemic typhus and still more so to spotted fever, there is relatively little evidence of vascular damage in scrub typhus. Cerebral involvement is qualitatively similar to that in epidemic typhus, but the lesions are less numerous and the individual nodules are somewhat smaller and less conspicuous. Interstitial myocarditis, in contrast, is more constant and severe in scrub typhus than in either the epidemic disease or in spotted fever. In view of the intensity of the interstitial reaction, remarkably little evidence of muscle-cell involvement is observed. Endocardial involvement was found in a third of the cases. Interstitial pneumonitis of marked degree is not rare in scrub typhus, whereas it is seldom evident in epidemic typhus or spotted fever. In this respect the disease shows an apparent relation to Q fever, in which pneumonitis

is often the predominating feature. One other point of differentiation appeared in the lymph nodes, which frequently show necrosis in scrub typhus but rarely do so in the other rickettsial diseases.

Injury Due to Cold

The recent war offered abundant opportunities for studying injury due to exposure to low temperatures. Several closely related syndromes have been described under such titles as "trench foot,"²⁶ "immersion foot"²⁷ and "high-altitude frostbite"²⁸ in American, British and German journals. The similarities of clinical and pathological findings are great, and the differences inconstant, suggesting that the underlying tissue injury is similar regardless of the type of exposure and whether or not actual freezing of the tissue occurs. The most complete pathological study to date is that of Friedman²⁶ from the Army Institute of Pathology based on 14 cases of trench foot. The findings closely parallel those of Siegmund²⁹ in cases of frostbite on the German-Russian front and of Blackwood²⁷ in cases of immersion foot.

The initial reaction following cold injury of all types is a prolonged period of vasoconstriction. This is followed by a stage of intense hyperemia. In the majority of severe cases this is accompanied by edema and frequently by exudation and hemorrhage into the tissues. In severe cases necrosis develops, leading to wet or dry gangrene. Pathological investigation has been hampered because surgery is delayed as long as possible, and most amputation material has shown only late stages of the process. Friedman was fortunate in having at his disposal several extremities from men dying of other causes shortly after developing trench foot. He found in this early material constant changes in the skin, subcutaneous fat, blood vessels and nerves. In the skin intercellular and intracellular edema was found in the malpighian layer in the earliest stages, later, vesiculation or frank necrosis and mummification occurred. The skin appendages were often involved, particularly the coil glands. Degeneration of collagen and elastic fibers, which was frequent in the later stages, was inconstant in the earlier ones. Involvement of the deeper portion of the subcutaneous fat tissue was constant and surprisingly extensive in view of earlier reports. In acute stages leukocytic infiltration was prominent, and edema and even fibrinous exudation into the interlobular fibrous septums were observed. Later, atrophy of fat lobules, accumulation of foam cells and replacement fibrosis became frequent. Occasionally, oil cysts formed. It seems probable that the loss of this protective layer had much to do with the long persistent functional disability in some cases that escaped gangrene. Vascular abnormalities were constant. In the early stages extreme dilatation and engorgement of small vessels were evident, frequently in association with peri-

vascular hemorrhages. The next stage of involvement was the appearance of thrombotic masses of agglutinated red cells, relatively free from platelet debris and fibrin in comparison with ordinary thrombi. Angitis, although usually present, was not particularly severe. In later stages (thirty to forty days), organization of thrombi and endarterial intimal proliferation were usual. Muscle changes were inconspicuous in the early cases, but extensive atrophy was noted in late lesions. Nerves in the early cases showed swelling, edema and focal degeneration of axis cylinders and myelin. In later stages demyelination and perineurial fibrosis were observed. White and Warren³⁰ suggested that the latter was responsible for the persistent pain noted in certain cases. It was not possible, on the basis of the pathological evidence, to decide whether vascular or neural changes were primary.

Epidemic Hepatitis and Homologous Serum Jaundice

The pathology of epidemic hepatitis was comparatively unknown until the outbreak of World War II. Jaundice due to massive necrosis of the liver had been recognized as early as 1842 by Rokitsansky,³¹ who first described and named "acute yellow atrophy." It was, however, regarded as a uniformly fatal disease. Catarrhal jaundice was considered a benign and totally unrelated malady. Although the Scandinavians Flindt,³² Linstedt,³³ Ehrström³⁴ and Wallgren³⁵ and the Englishman Cockayne³⁶ successively pointed out at intervals from 1890 to 1930 the parallelism of incidence between catarrhal jaundice and atrophy of the liver, general medical opinion was essentially uninfluenced by their observations. The world-wide pandemic of hepatitis in the soldiers of all belligerent countries in the recent war has provided unlimited material for study. From the spring of 1942 to April, 1945, material from 296 fatal cases was submitted to the Army Institute of Pathology. The first 118 of these were reported by Lucké³⁷ in 1943. The succeeding 178 cases were subsequently reviewed by Lucké and Mallory.³⁸

Most fatal cases of hepatitis can be readily classified into one of two types, subacute and fulminant, which show corresponding variations in clinical and pathological findings. The subacute type was exemplified by the series of cases developing in the American Army in 1942, which was reported by Lucké. None of the patients died in less than ten days, a few survived for one hundred days or more, and the survival period in 60 per cent ranged from twenty to fifty days. In these cases the liver showed extensive but irregularly distributed necrosis and numerous, often large, yellow or green foci of regeneration. This is the condition that for years was classified as "idiopathic acute yellow atrophy." In the second series of cases, reviewed by Lucké and Mallory, the majority (53 per cent) of patients died in less than ten days, many in as short a period

as three or four days, and a few even before the onset of jaundice. In such cases the symptomatology is often predominantly cerebral. The hepatic necrosis is diffuse and massive and no evidence of regeneration is seen, but the process has occurred so fast that the liver has had little time to shrink and is often only slightly reduced in size. Frequently, the gross appearance is that of an exaggerated "nutmeg liver." Cases of this type have also been reported by Wood³⁹ in material derived from personnel of the United States Navy. Despite the difference in the two types, enough points of similarity and enough transitional forms are observed to make it certain that they are not two diseases but represent a wide range of reaction to the same fundamental disorder.

The significant pathology of the disease is centered in the liver. In both types two features are constantly found—extensive degeneration and necrosis of liver cells and inflammatory reaction, most evident in an infiltration of the periportal connective tissue, with histiocytes and smaller numbers of other wandering cells. The necrosis is widespread and uniform in the fulminant cases, and regeneration is minimal or absent. Of particular interest are the patients dying in two to four days, either before or shortly after the onset of jaundice. Total destruction of the liver parenchyma has already occurred, and it is difficult to escape the conclusion that severe hepatic involvement must have antedated the first clinical symptoms.

It is of interest to compare the clinicoanatomic classification of hepatitis described above with current epidemiologic classifications. Four types of the disease are recognized from the latter point of view: the sporadic and epidemic forms of the "naturally" acquired disease, homologous serum jaundice and arsphenamine hepatitis. No clinical differences have been established and studies of nonfatal cases by the biopsy technique⁴⁰⁻⁴² have likewise failed to provide grounds for distinction. Lucké and Mallory found that a majority of their fulminant cases occurred in wounded men who had received plasma or whole-blood transfusions from fifty to ninety days before the onset of symptoms of hepatitis. This range is within the accepted incubation period of homologous serum jaundice. On the other hand, nearly a third of the fulminant cases appeared in men who had never received infusions of human plasma. These findings were balanced, however, by Lucké's cases in 1942, all of which were of the subacute variety despite the fact that the majority were cases of homologous serum jaundice secondary to yellow-fever vaccination. It is evident that the spontaneous and the homologous serum cases may each run either a subacute or a fulminant course and that the method of infection is not the explanation of variations in clinicoanatomic type. If different viruses are involved,^{43, 44} they produce identical end results.

Since this report was submitted numerous other important studies from the Army Institute of Pathology have been published.⁴⁵

REFERENCES

- Rich A R and Gregory J E. Experimental evidence that lesions with basic characteristics of rheumatic carditis can result from anaphylactic hypersensitivity. *Bull Johns Hopkins Hosp* 73: 239-264, 1943.
- Swift H F. Rheumatic fever. *J A M A* 92: 2071-2083, 1929.
- Gross L, Loewe L, and Eliasoph B. Attempts to reproduce rheumatic fever in animals. *J Exper Med* 50: 41-65, 1929.
- Coburn A F. *The Factor of Infection in the Rheumatic State*. 228 pp. Baltimore: Williams & Wilkins Company, 1931.
- Klinge, F. Der "Rheumatismus"—Begriff in geschichtlicher Betrachtung. *Jahresk f ärstl Fortbild* 24: 1-16, 1933.
- Vaubel, E. Die Erweisüberempfindlichkeit (Gewebshypersensibilität) des Bindegewebes experimentelle Untersuchungen zur Erzeugung des rheumatischen Gewebsschadens im Herzen und in den Gelenken. *Beur z path Anat u z allg Path* 89: 374-418, 1932.
- Junghans, E. Weitere Untersuchungen über die hyperergische Carditis und Arteritis insbesondere die Aortitis. *Beur z path Anat u z allg Path* 92: 467-475, 1934.
- Bruun, E. *Experimental Investigations in Serum Allergy*. 229 pp. London: Oxford University Press, 1940.
- Rich, A R. Role of hypersensitivity in periarteritis nodosa as indicated by 7 cases developing during serum sickness and sulfonamide therapy. *Bull Johns Hopkins Hosp* 71: 123-140, 1942.
- Idem. Additional evidence of role of hypersensitivity in etiology of periarteritis nodosa: another case associated with sulfonamide reaction. *Bull Johns Hopkins Hosp* 71: 375-379, 1942.
- Rich, A R, and Gregory J E. Experimental demonstration that periarteritis nodosa is manifestation of hypersensitivity. *Bull Johns Hopkins Hosp* 72: 65-88, 1943.
- Idem. On anaphylactic nature of rheumatic pneumonitis. *Bull Johns Hopkins Hosp* 73: 465-478, 1943.
- Wilson C, and Byrom F B. Vicious circle in chronic Bright's disease. Experimental evidence from hypertensive rat. *Quart J Med* 10: 65-93, 1941.
- Smith, C C, Zeek P M, and McGuire J. Periarteritis nodosa in experimental hypertensive rats and dogs. *Am J Path* 20: 721-735, 1944.
- Klemperer, P, Pollack A D, and Baehr G. Pathology of disseminated lupus erythematosus. *Arch Path* 32: 569-631, 1941.
- Baehr, G, Klemperer, P, and Schiffrin, A. Diffuse disease of peripheral circulation usually associated with lupus erythematosus and endocarditis. *Tr A A Physicians* 50: 139-155, 1935.
- Gross, L. Cardiac lesions in Libman-Sacks disease with consideration of its relationship to acute diffuse lupus erythematosus. *Am J Path* 16: 375-408, 1940.
- Baggenstoss A H, and Rosenberg E F. Cardiac lesions associated with chronic infectious arthritis. *Arch. Int Med* 67: 241-258, 1941.
- Idem. Visceral lesions associated with chronic infectious (rheumatoid) arthritis. *Am J Path* 18: 772-782, 1942.
- Freund H A, Steiner, G, Leichtentritt, B, and Price A E. Peripheral nerves in chronic atrophic arthritis. *Am J Path* 18: 865-893, 1942.
- Steiner, G, Freund H A, Leichtentritt, B, and Maun, M E. Lesions of skeletal muscles in rheumatoid arthritis: nodular polymyositis. *Am J Path* 22: 103-146, 1946.
- Steiner, G. Perineuritic and polymyositic granulomatous nodules in rheumatoid arthritis. *Am J Path* 22: 646-1946.
- Golden, A. Pathologic anatomy of "atypical pneumonia: etiology undetermined": acute interstitial pneumonitis. *Arch Path* 38: 187-202, 1944.
- McCorde H A, and Muckenfuss R S. Similarity of virus pneumonia in animals to epidemic influenza and interstitial bronchopneumonia in man. *Am J Path* 9: 221-252, 1933.
- Allen, A C, and Spitz, S. Comparative study of pathology of scrub typhus (tsutsugamushi disease) and other rickettsial diseases. *Am J Path* 21: 603-681, 1945.
- Friedman N B. Pathology of trench foot. *Am J Path* 21: 387-433, 1945.
- Blackwood, W. Studies in pathology of human "immersion foot". *Brit J Surg* 31: 329-350, 1944.
- Davis L, Scarff, J E, Rogers N, and Dickinson M. High altitude frostbite: preliminary report. *Surg Gynec & Obst* 77: 561-575, 1943.
- Siegmund, H. Pathologische Anatomische Befunde bei örtlichen Kälteschädigungen mit Berücksichtigung der Spätschaden. *Zentralbl f Chir* 70: 1558-1570, 1943.
- White J C, and Warren S. Causes of pain in feet after prolonged immersion in cold water. *War Med* 5: 6-13, 1944.
- Rokitansky, C. *Lehrbuch der pathologischen Anatomie*. Third edition. Vienna: W Braumüller, 1861. Vol 3. P 269.
- Flinck N. Bemærkninger med Hensyn til den saakaldte katarralske Icterus's Aetologi og Genese. *Bihol f læger* 1: 420-452, 1890.
- Linsædt F. Beitrag zur Kenntnis des Icterus catarrhalis mit besonderer Rücksicht auf die Inkubationszeit dessen epidemischen Formen. *Nord med Ark* 51: Afd 2: 583, 1919.
- Ehrström R. Icterus catarrhalis, akute gelbe Leberatrophie und chronische Hepatitis als Ausprägungen derselben Krankheit, Hepatitis epidemica. *Acta med Scandinavica* 65: 573-581, 1927.
- Wallgren, A. Erfahrungen über epidemischen Icterus (sog Icterus catarrhalis). *Acta pathol (Supp)* 2: 9-190, 1930.
- Cockayne E A. Catarrhal jaundice, sporadic and epidemic, and its relation to acute yellow atrophy of liver. *Quart J Med* 6: 1-28, 1912.
- Lucké B. Pathology of fatal epidemic hepatitis. *Am J Path* 20: 471-593, 1944.
- Lucké, B, and Mallory, T B. Fulminant form of epidemic hepatitis. *Am J Path* 22: 867-945, 1946.

- 9 Wood, D. A., Pathologic aspects of acute epidemic hepatitis with especial reference to early stages: report of series of ten cases including case in which there was spontaneous rupture of spleen and six cases of fulminating disease in patients who had been wounded several months previously *Arch Path* 41 345-375 1946.
10. Roholm, K., and Iversen, P. Changes in liver in acute epidemic hepatitis (catarrhal jaundice) based on 38 aspiration biopsies. *Acta path. et microbiol. Scandinavica* 16 427-442 1939
- 41 Dible J H McMichael J and Sherlock S P V Pathology of acute hepatitis aspiration biopsy studies of epidemic arsenotherapy and serum jaundice *Lancet* 2 402-408 1943

- 42 Azenfeld H., and Brass K. Klinische und biopsische Untersuchungen über den sogenannten Icterus catarrhalis. *Frankfurt Ztschr f Path* 57 147-236 1942.
- 43 Paul J R., Havens W P., Jr., Sabin A B and Philip, C. B. Transmission experiments in serum jaundice and infectious hepatitis *J A M A* 128-911 915 1945
- 44 Neefe J R., Stokes, J., Jr., and Gellis, S. S. Homologous serum hepatitis and infectious (epidemic) hepatitis: experimental study of immunity and cross immunity in volunteers preliminary report *Am J M Sc* 210 561-575 1945
- 45 Contributions from Army Institute of Pathology *Mil Surgeon* 99 363 740 1946

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

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CASE 33121

PRESENTATION OF CASE

First admission A sixty-four-year-old English wool dealer was admitted to the hospital because of severe nausea and vomiting of one day's duration. He had had no pain, hematemesis or any change in bowel habits.

Physical examination was entirely negative except for a blood pressure of 170 systolic, 95 diastolic. Two urine examinations showed a +++ test for albumin with many white cells and bacteria in the sediment. Examination of the blood showed a hemoglobin of 14.2 gm and a white-cell count of 11,200, with 84 per cent neutrophils. A gastrointestinal series revealed a diverticulum projecting medially from the second portion of the duodenum. Recuperation was spontaneous, and the patient was discharged four days after admission.

Final admission (eight months later) During the night before admission the patient became restless and nauseated but did not vomit. At 7.30 a.m. a severe, sharp pain, "like a rifle shot," developed under the "breast bone" and in the throat. This was associated with shortness of breath, and about four hours later the pain radiated down the arms and into the back between the scapulas.

Physical examination revealed a pale man who was slightly obese but not short of breath. The pulse was 112 and of good quality and the blood pressure was 128 systolic, 90 diastolic. The neck veins were distended and pulsating while the patient was lying down. The heart did not appear enlarged. The aortic second sound was equal in intensity to the pulmonic second sound, and there were no murmurs. The cardiac sounds were somewhat decreased in intensity. The chest was clear, and the abdomen normal. There was slight cyanosis of the

finger-nails, but no peripheral edema. An electrocardiogram three and a half hours after the onset of the attack was within normal limits. At 1.30 p.m. on the day of admission the patient had a convulsion, the pulse became weak and irregular and the blood pressure could not be obtained. Oxygen and 0.5 cc of adrenalin were administered, but the pulse finally became imperceptible and the patient expired.

DIFFERENTIAL DIAGNOSIS

DR CONGER WILLIAMS From the data presented, I cannot reach any conclusion about the illness that caused the first hospital admission, and I doubt whether this episode had any relation to the final acute illness. Possibly, the urinary findings can be explained by urinary infection, although a widespread disease affecting both the kidneys and the heart, such as periarteritis nodosa, should not be overlooked. The one value of the examination at the first admission is to establish the fact that the blood pressure was slightly elevated. It may be of some importance in determining the cause of the final episode.

At this point it is well to consider what conditions caused the acute pain in the chest. First of all, in a man of this age, the possibility of coronary heart disease with acute infarction must always be considered. In favor of that diagnosis is the fact that the pain was located beneath the sternum and radiated up into the throat, later going into the arms. This may have happened when the pain increased in intensity. The drop in the systolic blood pressure to 128 from the former level of 170 is also consistent with infarction. Against the diagnosis is the quality of the pain, which was described as sharp. The characteristic pain of myocardial infarction is dull or squeezing, often described as a sensation of pressure. Some patients in describing pain, however, use the adjective "sharp" to mean severe rather than knife-like. It is possible that some confusion arose merely from the choice of terms in description. Another point against the diagnosis of infarction is the apparent suddenness of onset of severe pain, although the restlessness during the preceding night may have marked the real beginning of the trouble. Also, whereas radiation of pain into the back occurs with myocardial infarction in a fair percentage of cases, I think that radiation of pain from the sternum into the neck, down both arms and into the back — during the course of one attack — is rather unusual. Repeated attacks may occur in which the radiation of pain

varies, but I believe that this was an unusually wide referral of pain for a case of infarction.

Certainly, in any acute emergency giving rise to chest pain, the possibility of dissecting aortic aneurysm should be considered. In the first place we know that this patient had hypertension, which can almost be called a necessary prelude to dissection. Secondly, the onset and intensity of the pain in the chest are both more in favor of dissecting aneurysm than of myocardial infarction. If it is assumed that the first pain, described as substernal and radiating into the neck, was produced by involvement of the mouths of the coronary arteries in the progress of dissection, it might be said that the pain in the back, instead of being referred pain, represented extension of the dissection along the course of the aorta down into the descending portion. Another point that should be mentioned and is perhaps slightly against the diagnosis although not ruling it out is the fall of the blood pressure. Usually, in acute dissection the blood pressure is surprisingly well sustained. I shall say more about that later.

Apparently, in the history a statement was made about shortness of breath. That should be clarified. The patient may have meant that he had sufficient substernal discomfort to produce a sensation of shortness of breath, which is quite different from dyspnea. I assume that he did not have dyspnea because it was not evident on physical examination.

The finding of distended and pulsating neck veins is not necessarily significant with the patient in the horizontal position. The fact that this man may have had increased venous pressure should be considered, however, and its implications should not be overlooked. If he actually had an increase in peripheral venous pressure, what conditions were responsible? I should like to mention three, as being the likeliest. The first is congestive heart failure, for which evidence is practically nonexistent in this case. Although shortness of breath was mentioned, it was not observed on physical examination. The lungs were clear, and we have nothing except this one finding to suggest failure of the myocardium. Another condition that produces an acute, sudden increase in peripheral venous pressure is cardiac tamponade. This, of course, is a frequent complication of dissection of the aorta that progresses down through the root of the aorta, with rupture into the pericardial sac. Also, the break may occur above the base of the aorta but below the attachment of the pericardium to the aorta. Therefore, that is a possibility. If the leak is small, death does not necessarily ensue immediately — the patient may survive for several hours. If there is an increase in venous pressure as a result of acute cardiac tamponade, pulsus paradoxus is usually evident on examination. It is possible to miss a paradoxical pulse, however, if the measurement is made simply by palpation of the radial artery. It is

sometimes necessary to use auscultation to detect pulsus paradoxus. Acute pericardial tamponade would also explain the fall in blood pressure. The third possibility to explain the increase in venous pressure is pulmonary embolism. I find nothing to support that diagnosis, and if this man had pulmonary embolism, the widespread pain must be explained on the basis of a secondary myocardial infarction. Pulmonary embolism complicated by myocardial infarction is not too rare, but I discard that possibility in this case.

The normal electrocardiogram is slightly against the diagnosis of myocardial infarction but by no means rules it out. It is possible to have a large infarction with no change in the electrocardiographic findings for hours or even days.

There are several possibilities to explain the sudden exitus. Dissection could have involved the cerebral vessels, producing convulsions. Or this may have been caused by cardiac arrest, either from auriculoventricular block — the so-called "Adams-Stokes phenomenon" — or from ventricular fibrillation. Another possibility is a sudden massive hemorrhage that, by producing acute cerebral anoxia, may also have caused the convulsions. A frequent termination of aortic dissection is rupture into the pleural cavity, with massive hemorrhage. Besides aortic aneurysm and myocardial infarction, I considered the other conditions that one usually thinks of in the differential diagnosis of acute chest pain. Those included acute pancreatitis, which I discarded because of the absence of abdominal findings and also because of the absence of vomiting on the final admission. I do not believe that any of the acute pulmonary episodes, such as pulmonary collapse, pneumothorax and mediastinal emphysema, explain the history as given or the radiation of pain into the arms, neck and back.

In conclusion my diagnosis is dissecting aortic aneurysm, mostly on the basis of the history. I realize that several of the positive findings one likes to see, such as the rapid development of an aortic diastolic murmur and absent pulsations in one or more of the limbs, were not present.

DR BENJAMIN CASTLEMAN Have you anything to add, Dr White?

DR PAUL D WHITE The fact that the neck veins were pulsating as well as distended helps to rule out any large mass, such as hemorrhage, compressing the mediastinal vessels. In such a case I should expect that there would be distention but not pulsation in the vessels.

CLINICAL DIAGNOSIS

Dissecting aneurysm of aorta?

DR WILLIAMS'S DIAGNOSIS

Dissecting aneurysm of aorta

ANATOMICAL DIAGNOSES

Dissecting aneurysm of aorta, with rupture into pericardium
Cardiac tamponade
 Chronic pyelonephritis left kidney

PATHOLOGICAL DISCUSSION

DR CASTLEMAN Autopsy showed everything that Dr Williams predicted. This was a dissecting aortic aneurysm. The intimal tear had occurred about 15 cm above the aortic valve and had dissected proximally down around the coronary mouths. Although at the time of autopsy little blood was found in the dissecting channel, there was separation down to and around the coronary mouths, which may explain the anginal attacks. The aneurysm had extended distally along the arch and the descending aorta into the left iliac artery. It surrounded and extended into one of the renal arteries. The external tear was not easy to make out, but we know that it occurred within the pericardium because the pericardial cavity was filled with blood. The fact that we could not find the actual tear indicates that there may have been a slow leak over a period of two or three hours. That might account, as Dr Williams suggested, for the distention of the neck veins. Another interesting finding—one that we have seen in a number of cases with pericardial hemorrhage—was extravasation of blood into the adventitia of the pulmonary arteries. This blood extended along and formed a hemorrhagic extravasation in the subpleural space, especially in the interlobar septums. This may also have added to the distention of the neck veins.

The only other finding of note was a chronic left pyelonephritis, which probably accounted for the urinary findings found at the final admission.

DR HOWARD B. SPRAGUE There is one point of interest in this case that I wish to bring out. I did not see the patient myself, but asked Dr William C. Bridges to see him on an emergency call. I discovered later that this man had attended an annual banquet of the wool trade on the previous night. His friends told me that he appeared perfectly well and that they could not understand how such a healthy person could be dead the next day. He was active in business, making frequent trips abroad, and was free from symptoms. The incident tends to spread the belief among laymen that heart disease strikes without warning. As a matter of fact, most patients dying of coronary disease have warnings of an anginal character for some time prior to the fatal attack. Lack of such symptoms is further evidence, therefore, in favor of dissecting aneurysm as against coronary occlusion, although the rule does not hold in every case. Whether or not the heavy banquet was a factor in precipitating the aortic rupture, one cannot say.

DR WHITE It is of some importance, particularly in treatment, to differentiate as soon as possible myocardial infarction and dissecting aortic aneurysm. From the standpoint of prognosis the chances are ten to one of recovery from myocardial infarction and ten to one against recovery from a dissecting aneurysm. That is approximate, of course.

CASE 33122

PRESENTATION OF CASE

A fifty-year-old woman was admitted to the hospital because of palpitation, dyspnea and orthopnea.

She had been treated by a physician for high blood pressure and "sick headaches" for many years. Five years before entry, because of profuse menstrual periods and intermenstrual bleeding, a hysterectomy had been performed for fibroids of the uterus. Adrenalin given preoperatively caused palpitation. After operation the physician told the patient that she must have had rheumatic fever in childhood because the aortic valve was "all eaten away" and the heart was "greatly swollen." An attack of phlebitis in the left leg subsequently forced the patient to remain in bed for a month. At that time she began to have orthopnea and exertional dyspnea and palpitation. There was no ankle edema, cyanosis or cough. Digitalis was administered, and the dyspnea cleared, the patient was able to return to her household duties after a month or two. She continued to notice exertional dyspnea and palpitation, however, and was forced to lead a rather sedentary life. Her condition remained unchanged until four months before admission, when the lower teeth were extracted, and a week or two later there was a sudden brief attack of nausea, a dry hacking cough, soreness in the ribs and fever. The pounding of the heart became marked, and a severe ache developed in the right knee and calf, extending to the toes, which became swollen. The pain in the knee cleared a few days later, but there was persistence of fever and malaise. The patient was hospitalized and given penicillin, with considerable relief, but the nausea persisted when she returned home. She remained on a liquid diet because of inability to swallow solid food. She had frequent green loose stools that started while she was in the hospital and persisted despite the fact that for years previously she had taken daily laxatives because of constipation. She returned to the hospital, where x-ray studies of the stomach, bowel and gall bladder were reported as negative, and penicillin was again given for a week. She continued to have palpitation, exertional dyspnea, night sweats, orthopnea and dysphagia. A week before admission exquisite tenderness developed in the left calf and ankle and the left toes. The patient stated that, according to her physician, in the few weeks prior to admission the blood pressure had dropped to normal.

The past history revealed no definite rheumatic fever, chorea or scarlet fever. An operation for a

ruptured appendix had been performed about fifteen years previously. The patient had had two pregnancies, the first child died in early infancy, and the second did not survive a cesarean section. A sister had died of what had seemed to be carcinoma of the stomach.

On physical examination the apical impulse was 9 cm from the midsternal line in the fifth interspace. There were a high-pitched, Grade III apical systolic murmur, a loud blowing systolic murmur at the base, loudest at the aortic area and transmitted to both sides of the neck, and a systolic thrill in the aortic and pulmonic areas. One observer heard a diastolic murmur in the pulmonic area. There were scars of the right rectus muscle beneath which a vague doughy mass that felt like adhesions was noted. Marked tenderness in the right upper quadrant just beneath the costal margin prevented palpation of the liver, but to percussion the liver did not appear enlarged. Light palpation in the right upper quadrant elicited rebound tenderness in the left upper quadrant. Scattered small red lesions, a few of which resembled petechiae, were noted in the skin. A small petechia with a white center was noted beneath the conjunctiva of the right lower lid. The left leg was warmer than the right. Both calves were tender when squeezed, the left more so than the right, and the left ankle was swollen and hot, without pitting edema. The ankle was quite tender. The toes of the left foot were markedly red and exquisitely tender, with erythematous patches, measuring 1 to 2 mm in diameter, over the left ankle and lateral aspect of the foot. Homans's sign was negative. There was no limitation of motion, and adequate pulsations were felt in the dorsalis pedis arteries bilaterally. There was questionable early clubbing of the fingers and toes.

The temperature was 99.6°F, the pulse 100, and the respirations 22. The blood pressure was 110 systolic, 64 diastolic.

Examination of the blood revealed a red-cell count of 5,150,000, with a hemoglobin of 13 gm, and a white-cell count of 10,200, with a normal differential count. The urine was normal. Plain films of the chest and abdomen were normal, the liver margin appeared normal. The total protein was 7.3 gm, the nonprotein nitrogen 30 mg, the uric acid 3.5 mg and the fasting blood sugar 107 mg per 100 cc. An electrocardiogram was normal on the fifth hospital day.

While the patient was in the hospital the blotches and the tenderness subsided somewhat, and a subsequent observation revealed absent pulsations of the right dorsalis pedis artery but equal pulsations were felt in the popliteal and femoral arteries on both sides. Blood cultures taken on the fourth hospital day grew colonies of alpha-hemolytic streptococcus. A week later the clubbing of the fingers became more pronounced, but no new petechiae developed. On the twelfth hospital day

examination of the heart revealed a Grade III aortic systolic murmur, with a thrill, and a Grade II aortic diastolic blow over the left sternal border, with no definite separate mitral murmurs. The hemoglobin at that time was 8.5 gm per 100 cc. Penicillin was given in a continuous drip starting on the sixteenth hospital day. On the eighteenth hospital day, however, the temperature rose to 103.5°F, and the patient was somewhat sleepy but euphoric when aroused. There were no localizing neurologic signs, but the following morning the patient complained of numbness of both hands, and there was some diminished tactile and position sense, especially on the left. She seemed somewhat confused throughout the day and spilled a glass of water on two occasions, presumably from the left hand. A test of the alpha-hemolytic streptococcus isolated by blood culture revealed that it grew in 0.25 units of penicillin per cubic centimeter and was inhibited by 0.5 units per cubic centimeter. Consequently, the penicillin dosage was increased to 1,000,000 units a day by intramuscular drip. Two days later the hands had cleared considerably, and a week later the patient seemed to be recovering. No new symptoms had developed.

The patient continued to run a temperature, occasionally as high as 101.5°F during the next few weeks, and on the forty-first hospital day she developed intermittent abdominal cramps, which were largely periumbilical, and by evening she vomited 400 cc of watery material. Examination revealed no acute abdominal tenderness or tympany, and peristaltic rushes could be heard concomitant with the pain. The temperature was 103.5°F, and the white-cell count 13,000. A plain film of the abdomen on the next day revealed distended loops of small intestine and a suggestion of a soft-tissue mass in the pelvis above the bladder shadow, more on the left than on the right, at which site the distention of the small bowel stopped. Fecal material was noted in the colon. Re-examination after the use of a Harris tube revealed the small intestine to be markedly deflated. Because of the continued pain and a rise in the white-cell count to 17,700, an exploratory laparotomy was done and adhesions were lysed. She appeared to recover from the operation, but spiking fevers continued on occasion. On the sixth postoperative day she had a mild headache, with numbness of one finger, and fever. On the following day the patient woke at 1.00 a.m. yelling incoherently. She was disoriented and recognized no one. She vomited recently ingested material once and put her hand to the left side of her head in a manner suggesting pain in this area. The neck was slightly stiff. The pupils were equal, the right pupil reacted sluggishly to light. The motor power in the extremities seemed equal, and she reacted to painful stimuli. No abnormal reflexes were encountered. She died about six hours later. The last positive blood culture had been obtained on the fifteenth

hospital day, and twelve subsequent blood cultures had been negative

DIFFERENTIAL DIAGNOSIS

DR JAMES H CURRENS The symptoms of palpitation, dyspnea and orthopnea are indicative of heart disease, probably due to limited myocardial reserve.

After the operation a physician told the patient that she must have had rheumatic fever in childhood because the aortic valve was "all eaten away" and the heart was "greatly swollen" This was the first evidence of valvular heart disease and was discovered when the patient was forty-six years of age

It is of interest that she had phlebitis of the left leg as a complication of the hysterectomy Phlebitis, particularly on the left, is not a rare complication of a pelvic operation, particularly hysterectomy Whether she had pulmonary emboli at that time to account for the increase in exertional dyspnea and palpitation is difficult to determine Certainly, the history is not specific on that point

The past history indicated a decreased cardiac reserve, probably on the basis of a decreased reserve of the left ventricular myocardium over a period of five years The appearance of fever two weeks after a dental extraction is important The fact that she developed fever and did poorly after the extraction of several teeth is a strong indication of the hazard of dental extraction in the presence of valvular heart disease It is our practice to give penicillin as a prophylactic measure to people with valvular and congenital heart disease before and for at least twelve hours after dental extractions I think that cough may be a somewhat neglected symptom in heart disease, but I fail to associate the cough in this patient with the subsequent events

It would be of interest to know whether the patient had pain with the diarrhea Presumably, she had none The night sweats are probably significant I interpret them as evidence of continued infection Tenderness in the left calf in the presence of a history of phlebitis of the left leg strongly suggests the recurrence of a thrombophlebitis in that leg

One wonders if the previous hypertension was merely systolic hypertension, possibly associated with some nervousness and palpitation of the heart The diastolic blood pressure of 64 is certainly normal, but in view of the findings it may have indicated a mild degree of aortic insufficiency

"The apical impulse was 9 cm from the midsternal line in the fifth interspace" Unfortunately, we do not know the position of the midclavicular line Since the impulse was in the fifth interspace, however, there was probably relatively little cardiac enlargement. I think that the auscultatory findings were quite characteristic of aortic stenosis as was the transmission of the systolic murmur to the apex The presence of a thrill in the pulmonary area is somewhat unusual, but if the thrill is strong enough,

it could be palpated well over the sternum and presumably on both sides of the sternum One observer heard a diastolic murmur in the pulmonic area That is probably a significant finding in view of the subsequent clear-cut aortic diastolic murmur

The vague doughy mass that felt like adhesions was a remarkable observation, but in view of the subsequent development of intestinal obstruction it presumably was correct

In any cardiac patient with pain or tenderness in the right upper quadrant one must think of liver congestion There is not much evidence in the physical findings, however, to suggest either systemic or pulmonary congestion Tenderness in the left upper quadrant, although the spleen was not palpable, may have been due to splenic infarction The other possibility, I suppose, is a mycotic aneurysm, but it is rather difficult to see how a mycotic aneurysm of the lower aorta or mesenteric artery could account for such pain

The observation of scattered small red lesions, a few of which resembled petechiae, is important if the diagnosis of subacute bacterial endocarditis is considered, and there is evidence strongly in favor of such a diagnosis I should interpret the pain in the left calf as having been due to phlebitis of the leg Homans's sign was negative That sign, however, is usually an early indication of phlebitis of the leg, so that it might easily be absent later on The finding of a petechia beneath the conjunctiva of the lower lid is an important positive sign when one is considering bacterial endocarditis The same thing should be said of the early clubbing of the fingers and toes

The laboratory data were normal throughout except for the borderline hemoglobin

It is unusual for an x-ray film of the heart to be normal in a person with the symptoms that this patient had I think that we had better see the x-ray films

DR RICHARD SCHATZKI In this film, which was taken ten weeks before death, the heart is not enormously enlarged, but I think that the left ventricle looks rounder than usual, as if there was some left ventricular hypertrophy

DR CURRENS Certainly, the heart was not greatly enlarged, and it makes me question to a large degree many of the symptoms that the patient had had in the past five years Left ventricular failure does not occur with a normal-sized heart She may well have had some cardiac neurosis complicating the organic heart disease

The disappearance of the pulsation of the right dorsalis pedis artery, with good pulsations above, suggests a small embolus in the right lower leg

The anemia may explain the more apparent aortic diastolic murmur that developed under observation Another explanation might be ulceration of the aortic-valve leaflets to allow greater insufficiency of the valve

On the eighteenth hospital day the temperature rose to 103.5°F, and the patient was somewhat sleepy but euphoric when aroused. A high temperature is an unusual finding in the presence of penicillin therapy. These findings are evidence, I should think, of embolism to the brain, resulting in "numbness of both hands and diminished tactile and position sense, especially on the left."

"A test of the alpha-hemolytic streptococcus isolated by blood culture revealed that it grew in 0.25 units of penicillin per cubic centimeter and was inhibited by 0.5 units per cubic centimeter." This indicates a moderately resistant organism and may or may not have been affected by the previous penicillin that the patient had received on two occasions.

I do not know how the patient died, since the record does not state what happened during the last six hours. She may have died in coma.

The primary diagnosis is certainly that of aortic valvular heart disease, with both stenosis and regurgitation. Although there was no history of rheumatic fever, rheumatic heart disease is the best bet so far as the etiology of the aortic stenosis is concerned. She was a little young for aortic stenosis presumably resulting from arteriosclerosis. I believe that this type of aortic stenosis is more frequent in men than in women. Another possibility is congenital heart disease with a bicuspid aortic valve. Perhaps the patient was too old for that, although patients with congenital bicuspid valvular disease live fairly long and not infrequently develop stenosis or regurgitation, or both.

The evidence for subacute bacterial endocarditis seems clear cut: fever, petechiae, anemia and bacteremia. There is good evidence for embolic phenomena to the brain and the right leg. The absence of splenomegaly certainly does not stand in the way of such a diagnosis. The complications of subacute bacterial endocarditis are of importance to consider. In patients who have been treated with penicillin in the last few years it has been possible to cure the bacterial infection in 65 to 70 per cent of cases if a sufficient amount was given. In 30 or 35 per cent of fatal cases, the patients die primarily of complications of one type or another, possibly of heart failure. The infection is rarely completely resistant if heroic doses of penicillin are used. In this case only 1,000,000 units of penicillin a day was given. If the infection is impossible to control, it is essential to increase the penicillin as much as possible. Doses as high as 30,000,000 or 40,000,000 units a day have been used. In this hospital I think that the largest dose used has been 10,000,000 units a day. Once penicillin is started it should be continued for at least three or four weeks. The two courses of penicillin for a week each before entry to this hospital were obviously ineffective in eradicating the infection, although they suppressed it temporarily.

The evidence for peripheral emboli is good. In bacterial endocarditis of the aortic valve, emboli occasionally enter a coronary artery.

I believe that this woman had aortic valvular disease with superimposed bacterial endocarditis and with embolic phenomena. It has been my impression that patients with bacterial endocarditis of the aortic valve are likelier to have emboli than those with infection on the mitral valve. The possibility of a mycotic aneurysm of the aorta, a cerebral artery, a mesenteric artery or an artery of the extremity remains good. A disturbing factor in this patient is that she continued to have fever and evidence of peripheral emboli. Mycotic aneurysms usually, of course, manifest themselves by rupture, resulting in a subarachnoid hemorrhage when the aneurysm is located in a cerebral artery.

Another possibility is that of active rheumatic fever. Perhaps 10 or 20 per cent of the cases with subacute bacterial endocarditis and rheumatic heart disease have evidence of active rheumatic fever during the course of the disease or at autopsy. It is conceivable that some of the pain in the left ankle and the continued fever were on the basis of active rheumatic fever. The joint pains, however, were not impressive, and one might expect evidence of more heart failure with active rheumatic fever. The electrocardiogram was normal, which is against active rheumatic fever, serious myocardial disease or hypertrophy. The evidence is quite good that the infection persisted either on the aortic valve or in an unrecognized mycotic aneurysm.

The fact that the organism was moderately resistant also suggests that penicillin did not cure the infection. Against such a diagnosis is, of course, the fact that the blood cultures were negative. It is conceivable that the infection had been suppressed temporarily by the penicillin but not eradicated. This observation was not infrequent in the use of the sulfonamides before the penicillin era, at which time the blood cultures often remained negative for days or weeks only to become positive again. Another possibility is a mixed bacterial infection of the aortic valve, which has been described by Organ and Poston*, conceivably penicillin might have eradicated only one of the organisms. I should interpret the final outcome in this patient as having been due to a persistence of infection either of the aortic valve or in a mycotic aneurysm.

She may or may not have had pulmonary emboli. The history is certainly not suggestive.

DR EDWARD F. BLAND: A low-grade fever during penicillin therapy sometimes disappears on cessation of the therapy and hence need not necessarily imply continued infection. Furthermore, even embolism may occur after the infection has been arrested.

*Organ, E. S. and Poston, M. A. Mixed infections in bacterial endocarditis. *Am. Heart J.* 23: 823-836, 1942.

DR CURRENS Have you ever seen a temperature of over 100°F with penicillin therapy for bacterial endocarditis?

DR BLAND I believe so

CLINICAL DIAGNOSES

Subacute bacterial endocarditis
Rheumatic heart disease
Cerebral embolus

DR CURRENS'S DIAGNOSES

Rheumatic heart disease, with aortic stenosis and regurgitation
Bacterial endocarditis, with either persistent infection or mycotic aneurysm

ANATOMICAL DIAGNOSES

Subacute bacterial endocarditis aortic valve
Cerebral mycotic aneurysm, with subarachnoid hemorrhage

PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY Post-mortem examination showed a normal-sized heart, but there was evidence of old rheumatic heart disease — slight on the mitral valve and quite definite on the aortic valve, with enough deformity to have produced

stenosis and probably a little regurgitation. There were vegetations on the aortic valve that were larger and more pliable than one sees in purely rheumatic heart disease but not so active as those observed in a subacute bacterial endocarditis. The immediate cause of death was an extensive subarachnoid hemorrhage. It is rather interesting that we found few manifestations of embolism. One can almost count on infarcts of the spleen and kidneys in cases of bacterial endocarditis. Both these organs were entirely free from any gross evidence of embolism. We could not tell whether histologically the vegetations on the aortic valve showed evidence of healing, since we decided to sacrifice the histologic studies for bacterial studies. The entire material of the valve was ground up and extensively cultured, but we were unable to grow out any organisms from the valve substance, so that it appears to have been bacteriologically sterile.

DR SCHATZKI How thick was the left ventricular wall?

DR MALLORY Of normal thickness. The heart weighed only 300 gm — a little on the small side.

DR JAMES H TOWNSEND What was the cause of the subarachnoid hemorrhage?

DR MALLORY There was a mycotic aneurysm.

DR BLAND Were there any Aschoff bodies?

DR MALLORY No.

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Formerly

The Boston Medical and Surgical Journal

Established 1828

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THE PROBLEM FAMILY IN BRITAIN

A RECENT editorial¹ expresses British concern for a lamentable social evil, the so-called "problem family" — a term used to describe a segment of the population sunk in poverty, ignorance and degradation, incapable of responding to improving influences and providing a reservoir of delinquency, vice and disease. Perhaps mindful of the record of Government participation in medical care and public health elsewhere in the British Commonwealth,² the editorial, although recognizing the need for some measure of corrective social legislation, points out that the apparatus for ameliorative action already exists and that a voluntary organization — the Society of Friends — has demonstrated an effective

approach to the situation treating the family as a unit, reconciling estranged members, rehabilitating the home and restoring self-respect. It endorses Brockington's³ program for reclaiming the problem family from hopeless destitution and degeneracy, this solution combines the authority of the magistrate and the personal, humanitarian approach of the social worker — the former places the family on probation and introduces the social worker, with whom the family co-operates in the hope of successfully completing the period of probation and thereby of retaining the children.

Brockington, observing that a great number of homeless children had been separated from their families because of parental cruelty, neglect and immorality, destitution, illegitimacy and lack of parental control, recommended that the problem family be reconstituted and placed under the supervision of health authorities before reaching the stage of enforced separation, and that authority be granted for registration of the problem family, rehabilitation of the home and appointment of special staffs for teaching and supervision. He further suggested that current legislation, with its tendency to break up the family, be amended to empower magistrates to remove the family as a unit to care and protection after the failure of probation, and emphasized the fact that delinquent children should be separated from their families only after child guidance and efforts to improve home conditions have failed.

The interest of the British medical profession in the problem family is to be commended. The constructive recommendations for prevention and amelioration without extensive social legislation merit careful attention in the United States, where similar families exist in disquieting plenty and where governmental paternalism is ever expanding. In medical sociology, as in other fields, organized medicine can influence the course and extent of Government intervention.

REFERENCES

- 1 Editorial. Problem families. *Lancet* 1:928, 1946.
- 2 Clemons, M. G. W. Changing face of medical practice in Tasmania. *M. J. Australia* 1:609-611, 1946.
- 3 Brockington, C. F. Homelessness in children: causes and prevention. Analysis of unparented children in three English counties. *Lancet* 1:933-936, 1946.

PREVENTABLE CANCER

ALTHOUGH it is true that the cause of cancer is unknown in most cases, it is equally true that the etiology in certain cases is obvious and that such cancers are therefore preventable. Into the latter class fall the occupational cancers arising in persons as the result of regular and prolonged contact with physical or chemical carcinogenic agents.

Such occupational neoplasms as the soot cancer of chimney sweeps and the cancer of the lung occurring in the Schneeberg miners have long been recognized. That malignant tumors of the bladder occur in workers in the aniline dye industry in the United States was not realized until 1932, and the fact that leukemoid conditions leading to death sometimes fol-

low exposure to benzol even in small amounts was not appreciated until even more recently. Cancer of the lung has been noted among workers in chromate plants and nickel refineries and among asbestos workers. Furthermore, it is said that cancer of the lung kills 75 to 80 per cent of unprotected cobalt workers, and carcinogenic properties have been found in such varied substances as arsenic, tar, crude mineral oil, shale oil, certain aromatic amines and, of course, roentgen rays and rays from radioactive substances.

It has been recommended that the medical profession, as well as employers and employees, be better educated regarding such carcinogenic agents and that special care be taken to guard the worker against them.* Medical supervision of those exposed to carcinogenic agents seems to be a wise step, and it is possible that some form of governmental inspection of industrial plants in which carcinogenic agents are used should be instituted. For example,

*Husper, W. C. Industrial management and occupational cancer
J A M A 131 738-741, 1946

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an intelligent college graduate who was clearly suffering from early myeloid metaplasia was recently seen by a physician who is particularly cognizant of these industrial hazards. The man categorically denied that benzol was used in the plant in which he worked, yet inspection by the proper state authorities a few days later showed that the plant reeked with benzol and that no precautions were being taken. Such conditions should not exist.

In connection with all occupational cancers it should be remembered that many years of exposure to a given carcinogenic agent may elapse before the malignant neoplasm makes itself manifest, and this very fact is likely to make both the employee and the employer lax in the matter of precautions taken. One should also remember that there are many individual variations in

the reactions of those exposed. Thus, in a family of four, all of whom were equally exposed to benzol over an equal period, one member died of myeloid metaplasia, one of a leukemoid disorder, and one of pancytopenia, the fourth member remained perfectly well, so far as could be ascertained.

Since an increasing number of carcinogenic agents are being found, both in the home and in industry, it behooves all of us to guard against their untoward reactions.

MASSACHUSETTS MEDICAL SOCIETY COMMITTEE ON ETHICS AND DISCIPLINE

Owing to a recent episode reported in the newspapers and involving one of the fellows of the Society, who suffered because of strict adherence to his interpretation of the "Code of Ethics" and the "Oath of Hippocrates," the following observation is offered:

Chapter II, Section 1, of the "Principles of Medical Ethics of the American Medical Association," reads as follows:

eventually developed keloids. Later the defendant told the plaintiff's husband that it was unfortunate, that a thing like that should not have happened and that the staff was going to take steps to correct it, and that apparently it had been caused by the solution's having been allowed to stay on the mat, thus exposing the skin, for too long a period. There was testimony by an expert called by the defendant that the burns were due to friction and pressure, that the use of Scott's solution was accepted obstetric practice and that the plaintiff's injuries were unavoidable.

The trial judge directed a verdict for the defendant on the ground that there was no evidence from which the jury could find that the defendant had been negligent. On appeal the Supreme Judicial Court said in part:

The jury could have found, in accordance with the defendant's admission, that the plaintiff's injuries were due to negligence, that there was no negligence on the part of the plaintiff or of any one other than the defendant, that, by the process of elimination, this negligence was that of the defendant. It is likewise no answer to say that the admissions were merely statements of regret, sympathy and benevolence evoked by human suffering.

The court ruled that the case should have gone to the jury, and the trial judge having directed a verdict for the defendant, a new trial was granted (*Woronka v S—*, Mass Adv Sh [1946] 1207).

CORRESPONDENCE

NEED FOR DIPHTHERIA IMMUNIZATION

To the Editor The number of cases of diphtheria in the City of Boston has continued to increase steadily. The Boston Health Department is making every effort through the press, radio and personal contact to notify all who are charged with the care of children that the number of cases is mounting and is alarmingly high and that immediate action must be taken to control the disease.

In the six years preceding 1946, there were 179 cases, with 10 deaths. In 1946, the corresponding numbers were 157 and 10. So far this year, 66 cases of diphtheria have developed in Boston. This is by far the greatest number of cases that has occurred in any two months during the last fifteen years. It indicates a trend in diphtheria that calls for an aggressive immunization program throughout the city.

This month, a city-wide campaign for diphtheria immunization is being conducted in Boston. Practicing physicians are urged to emphasize the need for diphtheria immunization and booster doses. The Boston Health Department is advocating that all children be taken to their own physicians or, where this is not practical, to the various clinics provided by the Health Department and by school authorities.

Studies indicate that children who have had original inoculations against diphtheria should be furnished booster doses of toxoid at intervals. The Boston Health Department in its clinics uses 0.5 cc of the toxoid supplied by the Massachusetts Department of Public Health, injected subcutaneously. This toxoid is available free of charge at all City of Boston culture stations.

JOHN H. CAULEY, M.D., M.P.H., Health Commissioner
Health Department
Haymarket Square
Boston 14

BOOK REVIEWS

The Extremities By Daniel P. Quiring, Ph.D., Beatrice A. Boyle, Erna L. Boroush, M.A., and Bernardine Lufkin, A.B. 8°, cloth, 117 pp., with 105 illustrations. Philadelphia: Lea and Febiger, 1945. \$2.75.

The simple line drawings of the origin, insertion, nerve and blood supply of the muscles of the extremities presented in this volume should be of great service to students and surgeons alike. It seems to the reviewer regrettable that the references are to Gray and Cunningham only, with none to the excellent textbook by Morris. This book is a product of the joint efforts of earnest students at the Cleveland Clinic Foundation. The extensive experience of the authors should serve well the needs of those interested in the functional principle of muscle action.

Physical Chemistry of Cells and Tissues By Rudolf Hober, M.D., J. B. Bateman, Ph.D., David R. Goddard, Ph.D., and Wallace O. Fenn, Ph.D. 8°, cloth, 676 pp. Philadelphia: Blakiston Company, 1945. \$9.00.

This is an extremely interesting and instructive book whose contents convincingly prove that physiology is deeply anchored in physical chemistry. The volume is arranged in sections as follows: selective principles of physical chemistry, large molecules, their physicochemical properties and their architectural and functional significance in living matter, introductory remarks concerning the architecture of protoplasm, the surface of the protoplast, its properties and its architecture, influence of some extracellular factors on cellular activity, the respiration of cells and tissues, contractility, and passive penetration and activity transfer in animal and plant tissues.

The volume has an excellent index of authors and subjects. Each chapter of each section is documented by excellent references. This should be a most useful book for physicians, chemists and physiologists.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Vitamins in Medicine By Franklin Bicknell, D.M., M.R.C.P., and Frederick Prescott, M.Sc., Ph.D., A.R.I.C., M.R.C.S., clinical research director, Wellcome Foundation, London. Second edition, revised and enlarged. 8°, cloth, 916 pp., with 208 illustrations. New York: Grune and Stratton, 1946. \$12.00.

This new edition of an English book has been revised by the rewriting and expansion of the chapters on the vitamin B complex and riboflavin. The other chapters have been brought up to date with the advances in knowledge of the vitamins. A new chapter has been added on the essential unsaturated fat-soluble acids (vitamin F) and minor fat-soluble vitamins. The references to the literature have been increased to four thousand five hundred, and the number of illustrations almost doubled. The printing is excellent, with a good type on good paper. A comprehensive subject index concludes the volume. This treatise should prove valuable as a reference source.

The Modern Attack on Tuberculosis By Henry D. Chadwick, M.D., and Alton S. Pope, M.D., deputy commissioner of public health, and director of the Division of Tuberculosis, Commonwealth of Massachusetts. Revised edition. 8°, cloth, 134 pp. New York: Commonwealth Fund, 1946. \$1.00.

This monograph was first published in 1942 and reprinted twice previous to this edition, which has been revised in the light of recent developments in administrative practice and in the technique of case finding and control. New material has been added, and some sections expanded, including photofluorography, the role of mass x-ray examination in industry and other population groups, with emphasis on the

ent role of an organized follow-up system, the financial aspects of hospitalization, rehabilitation, chemotherapy and the federal case-finding program. The volume is recommended for all persons interested in the tuberculosis problem in public health.

BC of Medical Treatment By E. Noble Chamberlain, M.D., M.Sc., F.R.C.P., lecturer in medicine, University of Liverpool, physician to outpatients, Royal Infirmary, Liverpool, and visiting physician, Smithtown Road Hospital. 12th edn, 206 pp. New York: Oxford University Press, 1946. \$3.00.

This small manual is designed for the general practitioner. A quick reference to the therapy of the ordinary diseases. The subject matter is arranged alphabetically, and a number of symptoms, such as pain and insomnia, have been included with the diseases. The book concludes with a fifty-eight-page chapter on diet by Miss Rose Simmonds, which includes any special diet sheets and tables.

Immunological Nonreaginic Food-Allergy By Arthur F. Coca, M.D., medical director, Lederle Laboratories. Second edition, 8th, cloth, 191 pp., with 28 tables. Springfield, Illinois: Charles C. Thomas, 1945. \$3.75.

The author presents in this monograph a method for the diagnosis and treatment of the relatively large groups of allergic diseases, such as migraine, urticaria, gastrointestinal disorders, neuralgias and other conditions hitherto unrecognized as allergic, in which the usual cutaneous tests almost invariably fail. Under the term "idioblastic allergy" are discussed the various aspects of food allergy. The concluding chapters are devoted to a discussion of the inheritance of food allergy, its relation to hypertension, its role in the causation of the common cold and its incidence in cases of cancer of the breast.

The Early Diagnosis of the Acute Abdomen By Zachary Lope, M.D., M.S. (Lond.), F.R.C.S. (Eng.), surgeon to St. Mary's Hospital, Paddington, and senior surgeon to Bellingroth Hospital, Wandsworth Common. Ninth edition, 8th, cloth, 262 pp., with 38 illustrations. New York: Oxford University Press, 1946. \$3.75.

The number of editions of this small manual, first published in 1921, speaks well for its popularity and soundness. This new edition contains only a few minor alterations and additions, but it should find a place in the libraries of all physicians and surgeons.

Psychological Medicine: A short introduction to psychiatry. With an appendix, "Psychiatry Associated with War Conditions." By Desmond Curran, M.B., F.R.C.P., D.P.M., psychiatrist and lecturer in psychologic medicine, St. George's Hospital, and Eric Guttman, M.D., M.R.C.P., neuro-psychiatric specialist, Emergency Medical Service. With a foreword by J. J. Conybeare, M.C., D.M. (Oxon.), F.R.C.P., physician to Guy's Hospital, London. Second edition, 8th, cloth, 246 pp., with 20 illustrations. Baltimore: Williams and Wilkins Company, 1945. \$3.50.

The authors have taken advantage of the need for a new edition of their manual to make an extensive revision of their text. A number of sections and chapters have been rewritten and enlarged. The principal changes are in the sections on constitutional factors, psychopathic personalities and the affective and hysterical syndromes. A chapter has been devoted to the obsessional states, and a brief discussion of psychomatic medicine has been included in the text. A short reading list concludes the volume.

Doctors East, Doctors West: An American physician's life in China. By Edward H. Hume, M.D., 8th, cloth, 278 pp. New York: W. W. Norton and Company, Incorporated, 1946. \$3.00.

Dr. Hume has written an interesting popular narrative of his twenty-five years' work in China. A graduate of Johns Hopkins University, stationed in India as an officer of the United States Public Health Service, he was persuaded by the Yale University Mission to go to Changsha, Hunan Province, in 1905, to establish a modern hospital and medical school. His work ended with the turning over of the hospital to the Chinese government in 1930. The story is valuable for the light it throws on medical practice and popular medical beliefs in China of the old days.

Journal of Gerontology: To add life to years, not just years to life. Volume I, 1946. 4th. Springfield, Illinois: Charles C. Thomas, 1946. Quarterly two parts. \$6.00 a year for both parts, \$3.00 a year for the nontechnical supplement.

This new journal on old age, its physiology, hygiene and diseases, the organ of the Gerontological Society, is a welcome addition to the field of special periodicals. The number of outstanding authorities comprising its editorial staff speaks well for its high standard of quality. The numbers are issued quarterly in two parts, technical and nontechnical. Each article in the former has summaries in English, French, Spanish and Russian. The nontechnical supplement is published for the general public and is written for the average reader who desires information on the subject. It contains abstracts of all the articles published in the technical part, rewritten in plain nontechnical language. It also contains discussions of current economic or social problems of the aged.

Advancing Fronts in Chemistry: A series of lectures sponsored by Wayne University under the direction of Neil E. Gordon, chairman, Department of Chemistry. Volume II: *Chemotherapy*. Edited by Wendell H. Powers, assistant professor of chemistry. 8th, cloth, 156 pp., with illustrations. New York: Reinhold Publishing Corporation, 1946. \$3.25.

This series of lectures discusses the following subjects: chemotherapy in experimental tuberculosis, synthetic antispasmodics, chemistry of the sulfonamides, the antimalarial problem, organometabolic compounds and the chemotherapy of parasitic diseases. Each lecture is well documented, with pertinent references to the literature. This volume is recommended for all medical-reference collections.

The Surgical Technic of Abdominal Operations. By Julius L. Spivack, M.D., LL.D., associate professor of surgery, University of Illinois College of Medicine, senior attending surgeon, Columbia Memorial Hospital, Chicago, and attending surgeon, Oak Forest Infirmary. Fourth edition, revised 8th, cloth, 710 pp., with 682 illustrations. Springfield, Illinois: Charles C. Thomas, 1946. \$10.00.

The first edition of this standard work was published in 1936, and the necessity for this fourth edition attests its popularity and soundness. The text has been revised by the elimination of some material and by the addition of new material. The type has been entirely reset. Selected bibliographies are appended to each chapter, and short historical sketches precede the discussion of each operation. The illustrations are clear and well executed. The book should prove valuable to surgeons and should be in all hospital and medical libraries.

NOTICES

NEW ENGLAND HEART ASSOCIATION

A meeting of the New England Heart Association will be held at Boston University School of Medicine auditorium, 78 East Concord Street, Boston, on Monday, March 31, at 8.15 p.m.

PROGRAM

A Note on Catheterization of the Coronary Sinus in Man and the Oxygen Content of Blood Obtained Therefrom. Drs. James W. Culbertson, Meyer H. Halperin and Robert W. Wilkins.

An Accurate Venographic Technic for the Study of Thromboembolic Disease of the Lower Extremities. Dr. George Mixer, Jr.

The Effects of Local Compression on Blood Flow in the Extremities of Man. Drs. Meyer H. Halperin, Carl K. Friedland and Robert W. Wilkins.

Adrenal Tumors and Hypertension. Drs. John B. Graham and Reginald H. Smithwick.

The Ventricular Gradient in Hypertension. Drs. Norman H. Boyer and William L. Hewitt.

Early Experiences with Total Thoracic Sympathectomy in Hypertensive Patients with Coronary Heart Disease and Angina Pectoris. Drs. Dera Kinsey and Reginald H. Smithwick.

The Effects of Sympathectomy on Certain Vasopressor Responses in Hypertensive Patients. Drs. Robert W. Wilkins and James W. Culbertson.

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The April 8 lecture of the Tuesday evening lecture series of the House Officers' Association of the Boston City Hospital will be held in the new Cheever Amphitheater, Dowling Building, at 7 00 Dr Wilder Penfield, director of the Montreal Neurological Institute, will speak on the subject, "Classification and Differential Diagnosis of the Epilepsies," which will be followed by a discussion by Dr William G Lennox

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Tuesday, April 1, at 8 15 p m Dr Philip E Meltzer will speak on the subject "Deafness Its management and recent advances in therapy"

AMERICAN COLLEGE OF SURGEONS

The sectional meeting of the American College of Surgeons, embracing the entire northeastern region of the United States, will open on Friday morning, March 28, at 8 30, and continue through Saturday afternoon, March 29, at the Providence-Biltmore Hotel, Providence Surgeons, members of the medical profession at large, medical students and hospital representatives from this area are invited to attend the sessions, which will begin each morning with the showing of medical motion pictures, followed by separate sessions for the medical and hospital delegates

The scientific session for the first morning will include the following talks "Surgery of Malignant Growths in the Neck," Dr William F MacFee of New York City, "Advances in Anesthesia," Dr Ralph M Tovell, of Hartford, "Surgery of Carcinoma of the Bladder," Dr Samuel N Vose, of Boston, and "Vascular Surgery," Dr Harris B Shumacker, Jr, of New Haven Luncheons for physicians, surgeons and hospital representatives, followed by a discussion of the subjects covered at the morning sessions, will be held on both days

Two panel discussions will feature the scientific sessions on the first afternoon The first, on fractures, will be conducted by Dr Robert M Yergason, of Hartford, with Dr Mather Cleveland, of New York City, and other prominent authorities serving as collaborators The other panel will be on intestinal obstruction and will be conducted by Dr Arthur W Allen, of Boston

A dinner will be held on the evening of the first day, followed by a premiere showing of a medical motion picture now under production and concluding with a reception

The talks at the scientific session on the second morning will be as follows "Use of Antibiotics in Surgical Practice," Dr Frank L Meleney, of New York City, "Surgery of Malignant Growths of the Neck," Dr Francis D Moore, of Boston, "Treatment of Portal Hypertension," Dr Arthur H Blake-more, of New York City, and "Management of Cancer of the Breast," Dr Frank E Adair, of New York City

The scientific-session program for the second afternoon will consist of panel discussions on postoperative care and on carcinoma of the colon The moderator of the first panel will be Dr John H Mulholland, of New York City, with Dr James B Blodgett, of Boston, Dr Bliss B Clark, of New Britain, and Dr E A Rovenstine, of New York City, as collaborators The moderator of the second panel will be Dr Samuel C Harvey, of New Haven, and the collaborators, Drs Arthur W Allen and Richard B Cattell, of Boston

INDUSTRIAL HEALTH MEETINGS

A conclave of combined professional personnel in industrial health work will take place at the Hotel Statler, Buffalo, New York, April 26 through May 4 These meetings will represent the thirty-second annual gathering of the American Association of Industrial Physicians and Surgeons, the ninth annual conference of the American Conference of Governmental Industrial Hygienists, the eighth annual meeting of the American Industrial Hygiene Association, the fifth annual conference of the American Association of Industrial Nurses and the fourth annual meeting of the American Association of Industrial Dentists

The sessions will be replete with many new subjects of interest, including the following round-table discussions for physicians and nurses, a symposium on new problems in the developments of industrial hygiene, a discussion of state codes and industrial-hygiene administration, conferences on environmental control, clinics on fractures and traumatic surgery

with a symposium on back problems, hazards incident to use of the atomic bomb, tracer chemistry in toxicology research, progress in the teaching of industrial medicine in American medical schools, a panel discussion on new preventive measures in industry, and a panel discussion on the education of the nurse in industry Prominent speakers on important subjects will be featured at dinner sessions and other events, such as the Cummings Memorial Lecture and the presentation of the Knudsen Award for the most outstanding contribution to industrial medicine during the past year

Also available at this meeting will be the opportunity to inspect and study a splendid group of scientific and technical exhibits, with the most recent developments and medical department accessories

Further details and a copy of the preliminary program may be secured by writing to Dr Edward C Holmblad, American Association of Industrial Physicians and Surgeons, 28 East Jackson Blvd., Chicago 4 All hotel reservations are made by the Housing Bureau, Buffalo Convention and Tourism Bureau, Incorporated, 602 Genesee Building, Buffalo, New York

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The New England Journal of Medicine

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Volume 236

MARCH 27, 1947

Number 13

THE MEANING OF THE PATIENT TO THE HOSPITAL*

IDA M. CANNON, D. HUM. (HON.)†

BOSTON

THOSE of us to whom the old Ether Dome and its furnishings are familiar, need little imagination to picture the scene just a hundred years ago today, when the first public demonstration of anesthesia for a major surgical operation took place. From all descriptions that I have seen, the focus of attention was on the great surgeon, in his frock coat, who dared accept responsibility for operating under untried conditions, on Morton, the dentist, who produced the mysterious stuff, or on the skeptics in the amphitheater. The atmosphere must have been charged as courage and determination met incredulity and suspended ridicule. What must have been the emotions of Gilbert Abbott, the patient, who participated so vitally in this adventure, which happily we can celebrate today? We know little of Gilbert Abbott besides the fact that he came to the hospital for treatment of a tumor of the jaw. But we can readily imagine him as a patient in the old Bulfinch ward and, on the fateful day, as being taken up the stairs to the operating room and placed on a plush operating table.

I suspect that Abbott, like most surgical patients since his time, experienced fear as he faced the oblivion of anesthesia. That he had courage we cannot question. His fortitude, like that of Dr. Warren, was a manifestation of character. But there was a difference, I believe, in the sources of their courage. Dr. Warren's bravery may well have been rooted in confidence in his own mature judgment and a willingness to risk ridicule for the sake of what success might mean to humanity in the future. The patient's courage, doubtless, was based on his faith in the surgeon who had cared for him and the hospital to which he had come for relief. Confidence of this order, which has been a large factor in making the Massachusetts General Hospital what it is today, is the greatest asset a hospital can have. It is not casually or easily earned. It is bred and maintained through consistent high quality of daily

service. Responsibility for holding it rests with everyone who has contact with patients. If standards of service are lowered, the trust of the patients and the public is shaken and may wither away. Confidence in this hospital's devotion to the primary purpose of care of patients not only has been the chief source of patients but also has done much in making possible the maintenance of the other purposes—namely, teaching and clinical research. We in social service have as our special concern the meaning of sickness and hospital experience to the patient. This gives us an opportunity to see the hospital rather objectively in terms of the layman, who is the patient. It also lets us see something of what the patient means to the hospital. I propose to test this theme in terms of the threefold purpose of this hospital—care of patients, teaching and research—and to suggest how these purposes give relevance to the growing social responsibilities of this great institution.

The needs of the sick were the reason why the hospital came into existence. Such obvious facts have a way of becoming dulled as we live with them. It is well to refresh them occasionally by bringing them into the focus of attention. Vivid descriptions of the neglect of the sick, as presented by the Rev. Mr. Bartlett and Drs. Warren and Jackson, brought forth generous gifts that made possible the construction of the Bulfinch Building. The dire state of the sick inmates of the almshouse evidently gave good Mr. Bartlett, the chaplain, sleepless nights, for it was he who stirred the "number of respectable gentlemen" to join with Dr. Warren and Dr. Jackson in the historic appeal to Boston citizens that is found in Bowditch's history of the hospital. This volume, which is one of my treasured possessions, is a dull book. But for a social worker, a few of its four hundred and forty-two pages are of extraordinary interest. Perusal of the Warren-Jackson letter gives an illuminating picture of the social conditions of Boston in those days. We note, on the one hand, the "worthy" citizens who considered themselves, in their affluence, as "treasurers of

*Presented at a symposium "The Hospital in the Community" held during the Ether Day Centenary of the Massachusetts General Hospital Boston, October 16, 1946.

†Formerly, chief of Social Service, Massachusetts General Hospital.

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IDA M. CANNON, D. HUM. (HON.)†

BOSTON

THOSE of us to whom the old Ether Dome and its furnishings are familiar, need little imagination to picture the scene just a hundred years ago today, when the first public demonstration of anesthesia for a major surgical operation took place. From all descriptions that I have seen, the focus of attention was on the great surgeon, in his frock coat, who dared accept responsibility for operating under untold conditions, on Morton, the dentist, who produced the mysterious stuff, or on the skeptics in the amphitheater. The atmosphere must have been charged as courage and determination met incredulity and suspended ridicule. What must have been the emotions of Gilbert Abbott, the patient, who participated so vitally in this adventure, which happily we can celebrate today? We know little of Gilbert Abbott besides the fact that he came to the hospital for treatment of a tumor of the jaw. But we can readily imagine him as a patient in the old Bulfinch ward and, on the fateful day, as being taken up the stairs to the operating room and placed on a plush operating table.

I suspect that Abbott, like most surgical patients since his time, experienced fear as he faced the oblivion of anesthesia. That he had courage we cannot question. His fortitude, like that of Dr. Warren, was a manifestation of character. But there was a difference, I believe, in the sources of their courage. Dr. Warren's bravery may well have been rooted in confidence in his own mature judgment and a willingness to risk ridicule for the sake of what success might mean to humanity in the future. The patient's courage, doubtless, was based on his faith in the surgeon who had cared for him and the hospital to which he had come for relief. Confidence of this order, which has been a large factor in making the Massachusetts General Hospital what it is today, is the greatest asset a hospital can have. It is not casually or easily earned. It is bred and maintained through consistent high quality of daily

service. Responsibility for holding it rests with everyone who has contact with patients. If standards of service are lowered, the trust of the patients and the public is shaken and may wither away. Confidence in this hospital's devotion to the primary purpose of care of patients not only has been the chief source of patients but also has done much in making possible the maintenance of the other purposes—namely, teaching and clinical research. We in social service have as our special concern the meaning of sickness and hospital experience to the patient. This gives us an opportunity to see the hospital rather objectively in terms of the layman, who is the patient. It also lets us see some of the old purpose of this hospital—care of patients, teaching and research—and to suggest how these purposes give relevance to the growing social responsibility of this great institution.

The needs of the sick were the reason why the hospital came into existence. Such obvious facts may have a way of becoming dulled as we live with them. It is well to refresh them occasionally by bringing them into the focus of attention. Vivid descriptions of the neglect of the sick, as presented by the Rev. Mr. Bartlett and Drs. Warren and Jackson, brought forth generous gifts that made possible the construction of the Bulfinch Building. The dire state of the sick inmates of the almshouse evidently gave good Mr. Bartlett, the chaplain, sleepless nights for it was he who stirred the "number of respectable gentlemen" to join with Dr. Warren and Dr. Jackson in the historic appeal to Boston citizens that is found in Bowditch's history of the hospital. This volume, which is one of my treasured possessions, is a dull book. But for a social worker, a few of its four hundred and forty-two pages are of extraordinary interest. Perusal of the Warren-Jackson letter gives an illuminating picture of the social conditions of Boston in those days. We note, on the one hand, the "worthy" citizens who considered themselves, in their affluence, as "treasurers of

*Presented at a symposium "The Hospital in the Community" held during the Ether Day Centenary of the Massachusetts General Hospital, Boston, October 16, 1946.

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God's bounty," with privileges of "indulgences in the true luxury of wealth, the pleasures of charity"—in contrast to the wretched poor in whose behalf the hospital was established. A hospital was frankly recognized as secondary to a good home for the care of the sick. But the insane presented difficulties even for a good home. In one of Mr Bartlett's early letters, he writes of their plight in terms to suggest a tragedy that might befall anyone. Referring to his experience with insane patients, he writes, "Several persons of respectability seized suddenly and brought to the almshouse were put in cells. Among them Capt Jones was put in a straight jacket." In those seafaring days this suggested a possible fate of our common humanity.

Again, in the Warren-Jackson letter, the housing conditions of the time are revealed. We read of the prospective patient who lived "in a garret or cellar, without light or due ventilation or open to the storms of inclement weather." There is no suggestion of a possible relation of social conditions and ill health. But we recognize an awakening of a humanitarian sense of responsibility for succoring those in trouble. Democracy was stirring, and from those beginnings, the hospital as a social institution has played an increasingly important role in our civilization. It has responded to the basic human needs more fully than any other of our institutions, since, with the growth and development of scientific medicine, the sick of all economic groups and in increasing numbers have turned to our hospitals for care.

The medical profession depends on lessons learned from the hard school of experience to improve its practice. It is a venture to say that this principle is not so truly characteristic of any other profession. Medicine, in its concern with questions of life and death, takes seriously the results of practice and builds up better methods as it looks frankly at success and failure.

Richard Cabot, in his early days as a clinic physician, confessed his failure to give adequate care to his patients. Scientific medicine as then organized and practiced in the outpatient department was lacking in many features essential for thorough examination and treatment. Dr Cabot gives a vivid description of his morning in the clinic in his *Foregrounds and Backgrounds in the Care of the Sick*. With the true sense of the artist that he was, he protests that the clinical picture "will run into confusion and distortion" unless the physician "backs his foreground view with the vista of the distant, the past and the future, the background of the community out of which this individual has emerged and to which he belongs." Again, he writes "Science without humanity becomes arid and finally discouraged. Humanity without science becomes scrappy and shallow." He puts these tests to himself as he faces the patient in his clinic.

Am I seeing the actual facts, the ever-new and unique facts, the crying and immediate needs as they come before me? Am I tracing out as far and as deep as I can the full bearing, the true lesson, the unseen spirit of this moment, this situation, this calamity, this illness? Am I using my eyes and ears, my sympathies and my imagination, as hard as I can? Am I searching for the deepest meaning, the widest bearing, the furthest connection of these facts?

Surely Dr Cabot realized that such comprehension and understanding were impossible for anyone certainly for the physician in the midst and under the pressures of a busy clinic—and that they could be approached only by teamwork of several specialists. But he threw a light on the still remote goal for all who participate in the care of patients. As a first step, the feeble beginnings of social service were initiated. The steady growth of this new adjunct of medicine is due to the soundness of Dr Cabot's concept that this special service was essential to the patient's best care. We learned gradually what the profession of social work might contribute through close and disciplinary co-operation with scientifically trained men. And we learned much from the patients themselves. Richard Cabot became an ardent advocate of case teaching in medicine. As we know, he carried this over into his clinicopathological conferences, which were characterized by frank, eager discussion free from any hampering assumptions of infallibility, since the group, teachers and students, analyzed failure as well as success in diagnosis and treatment.

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Confidence of the patient has a significant bearing on the teaching function of the hospital. In my years of experience at the Massachusetts General Hospital, I have learned how closely related are good care of patients and good clinical teaching. It is a satisfaction to be able to assure, with conviction, prospective patients and anxious relatives that the very presence of medical students means that the teachers are holding the care of the sick at a high level. In making this statement it is fitting to pay tribute to the "amenities of ward rounds," as exemplified by Dr Fred Shattuck, a great clinical teacher, and as expressed in word and deed by our Dr Means. Here, surely, is a tradition to cherish.

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simple Yet how tremendous has been the elaboration of each of them — care of the patient, teaching and research — through these momentous years! The irreducible minimum in clinical relation characteristic of the early days, that between the patient and the doctor, was soon increased to include “the kind and discreet nurse” I suspect that even today some patients come to the hospital expecting just such simple professional relations in the course of their care But how different is the reality! In the interest of better service, medicine has developed the complicated organization we now recognize as the modern hospital Nursing, as well as medicine, has been elaborated and specialized The rest of us — dietitians, medical social workers, occupational and physical therapists and laboratory technicians — present the patient with a most complicated environment just when simplification in human relations would be most welcome How important it is that this complex organization should run smoothly! That patients submit and in turn seek the beneficence of the hospital is due, I believe, to their confidence that the staff with all its variety holds to the spirit of the primary purpose of the care of patients The multiple teaching program of this hospital, where all these workers have their practical training, testifies to the acceptance of these supplementary services as essential to a high quality of medical care

The patient is the foundation for clinical research Many unknowingly have contributed to medical knowledge And many patients, such as those in Ward 4, have consciously taken part in the advance of medicine Captain Martell's glowing spirit has brought forth many eloquent expressions of appreciation for his generous and selfless offering of his obscure disease for a better understanding of diagnosis and operative procedure for parathyroid tumor The hospital's annual report for 1932 gave a unique and eloquent tribute to the Captain And Dr Means has told his story in a recent issue of the *Harvard Alumni Bulletin* Many hundreds of patients have served as nobly, since the more baffling and less understood symptoms have been earnestly studied in the course of treatment Happily, out of these untold human dramas, has come much merciful help not only to the patients themselves but also to those who come later, for knowledge of the advances in medicine becomes widespread

The hospital ward has always offered what might be called a social laboratory, which if comprehended could have given evidence of the neglected social ills of the community Hospitals have come to play a role in this field only in recent years I have an illustration of a neglected opportunity A patient, Francis Choate, was admitted to our wards in July, 1851 The diagnosis was “necrosis of the jaw in a phosphorus worker” Sixty-one years later the record of this case was used to help promote the passage of the Esch Bill, prohibiting the use of white

phosphorus in the manufacture of matches This is how it happened In 1909, John Andrews, secretary of the American Association for Labor Legislation, came to me to ask if I could help him find early cases of “phossy jaw,” as it was called, which had long been known to be caused by exposure of workers to the processes of match manufacture Mr Andrews, working with Senator Esch, had collected evidence from 150 current cases of this disease He wanted to strengthen his evidence by showing how long this disease had been known but neglected in the United States whereas European countries had long since prohibited the use of white phosphorus in industry As was our habit in such a search, I went to Mrs Myers, who in a few hours produced Francis Choate's record The following is an abstract from the history, as contained in the hospital record of 1851

[The patient] has worked for 14 years on phosphorus in manufacture of matches dipping cards of matches into phosphorus The room in which he worked would be filled with the fumes of it and he used to sit with his head over the vessel from which it came He says not many can stand the work because of bronchial irritation which it excites Usually shift workers [The] teeth have dropped out Half a dozen fistulous openings along the jaw Masses of dead bone protrude into mouth from toothless jaw

The patient was discharged on July 26 and advised to go to the country and return at a later date He returned in November, and filed away in Treadwell vault is the final record, a vivid description of his wretched state, his death and the autopsy Shortly before his death the record tells us, “he dozes over the fire,” much to his comfort I trust Little could he realize that many decades later his case, along with overwhelming current statistical evidence, would finally stop what the *Congressional Record* of 1912 designated as “one of the most loathsome diseases of our civilization” In that year, the use of white phosphorus in match manufacture was prohibited, and a patent of a harmless substitute was surrendered for cancellation A method, safe and effective, was established for use by the men who work in the match industry

In the early days of social service, a sixteen-year-old Russian-Jewish girl was referred to me, with a request that we arrange for payment for a back brace, to correct a lateral scoliosis She had been working for over a year at a machine that called for repeated, frequent shifting of heavy levers from right to left When this was reported to the orthopedist, his comment was “a perfect case of occupational scoliosis,” and he urged her to change her job This advice disturbed the patient, for her earnings in the daytime left her free to go to school in the evening But she did change her job The interest of the Child Labor Committee was enlisted, and the factory inspectors ordered that this machine be run by a male operator thereafter All this was before the passage of the Industrial Accident Law and just before Dr Edsall came to the hospital and de-

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James Homer Wright on blood platelets and actinomycosis and the development of his blood stain, the classic studies of Aub on lead poisoning, leading on to studies by Albright on calcium metabolism, obscure bone diseases and the action of hormones, Bauer's studies of arthritis, the work of Means and his associates on the thyroid gland, the initial use of liver therapy by Minot, Dr Paul D White's development of cardiology, and the calorimetric studies of Dr. Fritz B Talbot. From the procession of skillful surgeons, it would be unfair to choose names, since all contributed something to the advance of aseptic surgery. It is justifiable, perhaps, to note the development of chest surgery by Robinson, Whittemore, Richardson and Churchill and of hip nailing by Smith-Petersen.

The Massachusetts General Hospital has trained over 1650 house pupils, house officers, interns and residents, who have carried the lessons learned here throughout the world and through four wars. Here was established the second school of nursing in the United States, with 3151 graduates forming the largest alumnae group of any nursing school. It was one of the first to provide accommodations for private patients and built the Baker Memorial, the first hospital for people of moderate means, on the basis of the principle of high-quality hospital care at cost and of medical care with limited fees. Thus, this hospital has pioneered in many fields. It has always placed the welfare and interest of the patient first and so has been quick to accept and adopt advances made in other fields. Its associations with Harvard University and the Massachusetts Institute of Technology have helped it to maintain an open mind and to retain a youthful spirit. It has surely developed what Harvey Cushing called the "soul of a hospital." It has been, and still is, all that a great hospital should be. It must and shall be preserved.

The survival of the voluntary hospital in the modern world is mentioned because, as Garrison states, "As we enter the machine age the salient fact about medicine is the trend toward socialization." This suggests increasing participation of government in hospital affairs. Much that follows can apply to all voluntary hospitals but especially to the small group of university-connected hospitals in which teaching and clinical and fundamental research, in addition to the care of patients, are carried on, of which the Massachusetts General Hospital is an example.

The problem of finances is primarily one of income, which is derived from two sources — annual gifts and payment for service rendered, either from patients as individuals or from organizations responsible for their care.

The anticipated deficits of voluntary hospitals, which were founded to provide care regardless of the ability of the patient to pay, have in the past been met through gifts and legacies from philan-

thropic citizens. This hospital has been particularly fortunate in its benefactors and yet it is confronted with annual deficits that threaten to consume its accumulated capital. If it is true to its principles it cannot meet this need solely by raising charges to patients since this would establish the precedent of making only the sick pay for the sick. Yet federal and state tax systems, through income and inheritance taxes, have seriously reduced the number of large individual gifts and legacies. How can they be replaced?

We are passing from a period in which the support of voluntary hospitals was considered to be the philanthropic duty solely of the well-to-do and rich to one in which it is believed that such institutions must be supported by their beneficiaries. Obviously, this means industry and labor, from a corporate standpoint, and employers and employees, from an individual standpoint. It is this conception that has produced so-called "community chests," which are built on the principle of supplementing the larger gifts of a relatively small group of citizens by many smaller donations from all classes. As corporate bodies receiving benefits, industrial concerns must support hospitals. Labor, through its unions, whose members also receive benefits, must now assume a similar share of responsibility. Likewise, as individuals, each worker and each member of management must make his contribution either to the hospital of his choice or to the community chest, from which it may be distributed to all hospitals in the community. If the voluntary hospital is to be retained it must be financially supported by its community.

We are proud of the generosity of Boston's citizens. We are proud of the accomplishments of the Greater Boston Community Fund, but the Fund has been woefully deficient in meeting the financial needs of the voluntary hospitals of Greater Boston. If it desires the continuation of these voluntary hospitals it must do more. The alternative is clear. Hospitals we must have for the care of the sick, for the teaching of doctors, nurses and others and for research. Shall it be a voluntary tax for the support of voluntary hospitals, or shall it be a federal tax for the support of governmental hospitals? In which way will the money go farthest?

A special group of industrial beneficiaries comprises the pharmaceutical manufacturers, which produce hospital supplies. Many are national in scope. The hospitals not only are the largest users of their products but also must be depended on as the laboratories in which new products are finally tested. The manufacturers should support hospital research, and their conception of research should be broad. Grants-in-aid should be made for specific problems, unrestricted gifts for general or fundamental research and, finally, grants for pharmaceutical research and free beds in recognition of the fact that the ultimate goal is the application of the result of the preliminary type of research to the patient. A drug may be

veloped the Industrial Clinic David Edsall had a fine critical sense of the importance of clinical evidence. He encouraged analysis of the patient's work as a regular procedure in history taking as a means of bringing to light possible exposure to industrial poisons, special strains or adverse conditions that might affect the clinical picture. In this way, he often arrived at a more accurate diagnosis. He was also able, at times, with facts in hand, to demonstrate to industrial managers the evil effects of some of their processes on the human organism.

Hospitals have become, rather reluctantly, one of the best indexes of community health. I say reluctantly, for I remember the resistance of the medical profession to comply, at first, with the public-health measures requiring reporting of diseases declared dangerous to public health. It required a major adjustment, since such reporting seemed to run contrary to the sacred tradition to hold information about patients inviolate. The potential patient became the object of preventive medicine and, as such, has drawn the hospital into his service on an ever broadening concept of responsibility. Psychiatry, through its deepening insights and understanding, is bringing to light the more subtle influences of our social and physical ill-health and our well-being.

Dr Harvey Cushing, in his delightful address at the Centenary Celebration, paid tribute to a long

line of doctors, nurses and employees who had created and maintained what he called the "personality of the hospital." We who have belonged to the Massachusetts General Hospital family know what he meant by that phrase. Intangible it is, and yet a reality to us. We sense certain characteristics of the Massachusetts General Hospital that have steadily carried on its traditions through the decades. The personality of this most human of institutions has been consistent but happily not static. It has matured through the years in constant interaction with the community to which it has devoted its beneficence. Clinical medicine and public-health programs are becoming more closely related as medical knowledge is more widely and practically applied. In this broadening sphere the hospital administrator has had to take and will increasingly have to assume leadership. But, as the full measure of social obligation of medical institutions is more clearly comprehended, we shall realize that responsibility rests on all of us — trustees, administrators, all the professional groups and personnel — and on the public to which we look for support. We shall build wisely if we remember that in the future as in the past our primary responsibility is to the patient for whom the hospital exists.

THE VOLUNTARY HOSPITAL — HOW CAN IT SURVIVE IN THE MODERN WORLD?*

NATHANIEL W. FAXON, M.D.†

BOSTON

IN 1811 the citizens of Boston, led by a minister, a physician and a surgeon, established the Massachusetts General Hospital. The McLean Hospital, for patients with mental diseases, was opened in 1818, and the hospital for medical and surgical illnesses in 1821. Thus was sickness divorced from poverty and crime, from the almshouse and the prison.

The first state hospital, the Worcester Lunatic Hospital, was not built until 1830, twelve years after McLean Hospital, the Boston City Hospital was opened in 1864, forty-three years after the Massachusetts General Hospital. Thus did private foresight, initiative and action precede political recognition. What happened in Massachusetts happened elsewhere in the United States. Private philanthropy and private agencies have almost universally pioneered in medical and social needs that, when demonstrated, have often but not always been

accepted in whole or in part by government. Non-profit or, as they are usually designated, "voluntary hospitals" have been the pacemakers that have set the standards and made the advances. In such hospitals lie our hope and our security.

A consideration of what has been accomplished in this institution alone is illuminating: the demonstration of ether as an anesthetic, a boon accepted but scarcely appreciated by you who gather here to celebrate the centenary of this epoch-making event, the discovery of the Y ligament and a new method for reduction of dislocation of the hip, by Dr Bigelow, the recognition of appendicitis, leading to a rational and successful method of operative treatment, by Dr Reginald Fitz, Shattuck's revolutionary treatment of typhoid fever, the establishment of Social Service, by Dr Richard Cabot, the long fight of Amory Codman to awaken interest in and acceptance of end results and the true evaluation of the success of surgical or medical treatment, recognition of the importance of pathology through the erection of one of the first, if not the first, pathological buildings and the work therein of Dr

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†Director, Massachusetts General Hospital and Massachusetts Eye and Ear Infirmary.

No third party has yet paid in full all hospital costs, and the deficit has been met by the hospital from income from endowment, gifts of individuals and grants from the Greater Boston Community Chest. Certainly, the contribution of the Massachusetts General Hospital toward the care of patients for whom state and federal agencies are responsible and for cases under the Workmen's Compensation Act is over \$100,000 a year.

What should be the relation of the hospital to these responsible agencies? The problem cannot be solved by a refusal to admit such patients. No hospital worthy of its name can refuse admission to patients in real need of treatment, with critical illness or following accidents, so that such patients will always be found in this hospital.

The argument that the hospital gets more for an indigent patient than it would if the patient alone was responsible and that for industrial accidents the Workmen's Compensation Act assures the hospital of some payment, whereas before the act was passed the hospital often got nothing, is a specious half truth. If government is responsible, should it not assume full responsibility? Should the hospitals subsidize industry and insurance companies? Regardless of what arrangements a hospital makes with individuals, using its own funds to make up deficits, should responsible governmental agencies likewise become beneficiaries of hospital charity? Should a situation be continued by which endowments given for "the care of the sick poor" or "for free beds" and donations to the Community Chest are used to defray expenses of the Department of Public Welfare or the Children's Bureau?

Thus, there are two conflicting ideologies. On the one hand, a hospital asks that government pay the full cost of care for any patient in any hospital, that cost to be determined according to acceptable governmental accounting formulas, on the basis that such a cost is a true reflection of the care given and received, and on the other hand there is the desire of government to obtain care at as low a cost as possible and as a final safeguard, the establishment of a ceiling payment rate, so that it can approximate a maximum budget for hospital care.

The present situation can scarcely endure. New groups are brought under governmental care every few years. Health-insurance legislation, such as that proposed by the Wagner-Murray-Dingell Bill, is before Congress. This would include practically all residents of the United States. It would authorize payment to hospitals of "not less than \$3 nor more than \$6 for each day for hospitalization not in excess of thirty days," for services that cost the Massachusetts General Hospital \$11. Even if this hospital was granted the right to charge patients the difference between the Government payment of \$6 and the cost of care, I doubt whether it could collect, because people would believe that the Government had promised them hospital care at

no cost in return for the wage deductions for health insurance. How could hospitals provide a subsidy of such an amount on all patients?

There are three possible solutions that hospitals continue to make up the difference between the cost of care and governmental payments, which, unless unexpected and unforeseen sources of income appear, is impossible, that hospitals provide less expensive and, therefore, presumably a lower grade of care for governmental beneficiaries — this is repugnant to physicians, hospital administrators and trustees, who have always striven to give medical care of the same quality, regardless of the patient's classification as ward, semi-private or private, the difference in hospital charge representing only a difference in luxury or privacy of hospital accommodations, and, moreover, an argument for the political demagogue is thus presented, and that the Government pay the full charge or cost of care. That the Government is beginning to recognize the justice of this last request is evidenced by the stand taken by certain federal agencies, but it has not been generally accepted by all agencies or by any state departments.

The high cost of hospital care is a frequent criticism of our hospital system, so that a word regarding costs is perhaps appropriate. The costs for each patient a day advanced from \$1 in 1857 to \$11 in 1945. During the same period, however, the current income per capita rose from \$140 in 1857 to \$1037 in 1943. This is nearly the same ratio of increase, so that although a patient had to pay eleven times as much for hospital care, he had a proportional increase in income with which to pay it.

Hospital costs vary to a considerable degree in different institutions. In the voluntary general hospitals of Boston the range is from \$8 to \$11. Costs are highest in teaching hospitals connected with medical schools. They must have extensive "readiness to serve" equipment, such as laboratories of all sorts, x-ray facilities and physical therapy. They must be prepared to receive patients at any hour, with operative personnel available if needed. They receive the most difficult cases. They develop and refine most of the advances in medical care, and pioneering is always expensive. Lastly, there is some expense, difficult to separate from operating costs, chargeable to teaching medical students, interns, residents, nurses, social workers, dietitians, technicians, physical therapists and others, and this is the hospital's contribution to education. Regardless of cost, it is essential that these groups be taught and given practical training. This can only be carried on in a teaching hospital.

On the other hand, hospitals, including teaching hospitals, have been notorious for paying salaries and wages below the level paid for similar work in industry. Longer hours of work are usually required. Hospitals have ever been frugal buyers. It is therefore fair to assume that whatever the cost, it is not

efficient in a test tube but may fail to cure a human being. Only in hospitals safeguarded and controlled by an efficient and watchful staff can the final test be made. *Hospitals deserve the generous support of all pharmaceutical manufacturers.*

So much for financial support through donations.

The second part of the financial problem consists in return for services rendered, which must be divided into services for which individuals are responsible and those for which governmental or other agencies are responsible.

It is generally agreed that private patients should pay cost or even a little more than cost and that semi-private patients should pay full cost. These classes can be dismissed from further consideration, since they create no financial problem.

Hospitals have traditionally set the ward rate and charged individual patients less than the cost of care. Thus, the present ward charge in this area is \$6 a day for board, bed and general service — items that cost the hospital \$8 a day. Extras such as x-ray films, operating room and laboratory fees, usually billed at cost, total approximately \$3, making a daily cost to the hospital of about \$11. Thus, full-pay individual ward patients contribute \$9 for services costing \$11. About 40 per cent do so. Another 30 per cent pay only a part of this cost, whereas the remaining 30 per cent are free patients.

There is at present a divided opinion regarding whether hospitals should continue their traditional policy of setting ward charges lower than cost or whether charge and cost should be synonymous. According to the first method all ward patients are benefited or are, in other words, the recipients of charity, but by the same token, the greater the number of patients cared for, the greater the financial strain on the hospital. There has therefore been a growing inclination on the part of hospital administrators to make charges equal cost, recognizing that fewer people will be able to pay ward charges in full and that larger allowances or remittances will have to be made. The gain would be that all would have a clear idea of what hospital care really costs. Gifts would still be needed to make up the difference between what ward patients would be able to pay and the charges that they would be asked to pay.

Another situation is created when a third party enters into the transaction — for example, the Department of Public Welfare, responsible for the care of an indigent patient, or an insurance company, responsible under the Workmen's Compensation Act for the hospital care of a patient who has met with an industrial accident. In each instance this third party has been made responsible by law, under certain conditions, for hospitalization. The hospital now deals financially with the third party, not with the patient. In itself there is nothing reprehensible in third-party contracts. The trouble occurs when such parties do not meet their financial responsibilities in full. The government has a way

of legally accepting a responsibility and then passing part of the financial burden to hospitals. Agencies frequently profess to be willing to pay the rates charged to individual patients, but to date none has ever done so. There has always been a gap, even when the hospital charge was less than the cost. If charge and cost were synonymous, the discrepancy would be still greater.

During the past year the Massachusetts General Hospital has received patients from the following sources: state and local departments of welfare, responsible for the care of indigents, department beneficiaries under Old Age Assistance and Aid to Dependent Children Acts and those from the Division of the Care of the Blind and the Deaf, the Department of Correction — that is, from state reformatory schools and prisons, state and local departments of health, responsible for the care of patients with contagious disease, including selected cases of tuberculosis for operation and arthritic patients for study and treatment, the Massachusetts Department of Public Health, which is the local administrative body for the federal program for care of crippled children, the United States Public Health Service, which controls genitoinfectious diseases, the Emergency Maternity and Infant Care Program and the Vocational Rehabilitation Plan, and employees coming under the Workmen's Compensation Act, administered by the Industrial Accident Board. This is a formidable, although not complete, list of governmental agencies that, by law, must provide hospital care for their beneficiaries. Each decade sees the addition of new agencies so that the problem now under consideration is increasing.

The admission of patients coming under the jurisdiction of these agencies has resulted in the following financial situation. As pointed out above, it costs the Massachusetts General Hospital a total of \$11 a day for each ward patient. Public welfare and other state agencies pay \$5 a day, which means that the hospital is contributing more for the care of an indigent patient than the responsible governmental agency. In 1945 this cost to the hospital amounted to over \$50,000. The Industrial Accident Board approves hospital charges to insurance companies at the rate of \$4.75 a day, in addition to approximately \$3 for extras, making a total of \$7.75 a day, which means that the hospital is contributing \$3.25 a day for each patient in this category. Yet this is supposed to be an insurance plan supported by industry and not intended to be a charity. In 1945 this cost to the hospital amounted to over \$30,000. The Massachusetts Department of Public Health, administering the federal Program for Crippled Children, the Emergency Maternity and Infant Care Program and the Rehabilitation Program, pays \$8 a day, so that here too, although to a lesser degree, the hospital contributes \$3 a day to the care of patients supposedly provided for by a federal program.

ship devote seven years after graduation from medical school to special training and limited practice. For those who graduated from medical school after January, 1938, a year must be spent as an intern in an acceptable hospital and at least two years as a resident, as a full-time surgical assistant to a qualified surgeon or in an apprenticeship of equivalent value. More recently, the American College of Surgeons has further increased the period of hospital training for candidates who graduated after January 1, 1944, to a minimum of four years of hospital service and graduate study in the basic sciences. More specific is the American Board of Surgery,² which requires that applicants, before they are permitted to stand a written, clinical and laboratory examination, spend a minimum of five years devoted to surgical training after completion of a year of internship.

According to the American Medical Association,³ at the end of 1945 there were 6511 registered hospitals with a total bed capacity of 1,738,944, the actual utilization of beds being 10.6 per 1000 population. Hospital facilities are increasing both in proportion to the population and in actual numbers. The following figures are of significance⁴:

YEAR	BED CAPACITY
1930	1,000,000
1940	1,226,245
1945	1,738,944
1950	2,000,000 (estimated)

Of the 6511 registered hospitals, 4744 were general hospitals, 3066 of these had a capacity of 100 beds or less, 1148, a capacity of 100 to 300 beds, and 530, a capacity of 300 beds or more. The total capacity for the 4744 general hospitals was 922,549 beds. Of the 530 hospitals with a capacity of 300 beds or more, in which the average was about 1150 beds, less than 100 were in medical centers.⁴

In an attempt to determine the number of surgeons required in the future, it is necessary to consider the estimated increase in the total number of hospital beds that will be required during the next few years. From the figures cited above, it can be estimated that by 1950 there will be approximately 2,000,000 hospital beds. Indeed this will create an increase in the number of surgeons that will be required. The Committee on Graduate Training of the American College of Surgeons⁵ reported in 1939 that there were 6288 surgeons in the United States properly qualified and doing most of the surgery. In the same year, 231 hospitals were credited as having adequate facilities for training in surgery. These hospitals provided positions for 1234 surgeons in training. Also in the same year, 541 surgeons completed the training offered by these 231 hospitals, 145 having completed three years or more and 396 less than three years. It is evident, therefore, that only a limited number of this group would be eligible for examination by the American Board of Surgery or recognition by the American College

of Surgeons. In 1945 the American College of Surgeons⁶ reported that there were 249 hospitals in the United States and Canada conducting approved plans of graduate training in general surgery and the specialties. Two hundred and three of these were for general surgery. This information suggests that facilities for training in surgery had not kept pace with the increase in hospital beds. During the war years 1942-1945, however, surgical training was largely curtailed, and it may be expected that by 1950 there will be an increase in the facilities for training in surgery.

If 6300 surgeons were required to fulfill the needs of the country in 1939 and if the statistics are correct that 3 per cent of the total either die or retire from practice each year, it becomes apparent that a much larger number of completely trained surgeons will be required each year from now on. There must be not only replacements but also those to meet the increased demand because of the opening of new hospitals.

There are in the United States 69 approved medical schools, which for the most part make the best training hospitals and set the pace of hospital practice. The clinical sections of these medical schools contribute to the graduate training of the majority of men who are preparing to qualify for one of the boards. At present, the medical centers of the medical schools are the only hospitals that are properly equipped to provide for complete training in surgery including the basic sciences of anatomy, pathology and physiology.

These medical schools and their medical centers, however, are not adequate to provide training for the number of surgeons that are needed. They are specifically lacking in clinical facilities. And at the same time, in the non-medical-school hospitals, there is clinical material that could well be used for training purposes. The young physician who seeks training and has as his objective the requirements of the American Board of Surgery will find competition keen in the medical-school hospitals. If he turns to a nonacademic hospital his training is frequently less desirable because teaching facilities are lacking and in particular opportunities for work in anatomy, physiology and pathology are not available. Of course, some large hospitals compare favorably with those of the medical centers, but by and large this is not true for the majority of hospitals.

The trend to hospital practice and that toward a greater number of hospital beds indicate that there will be a demand for more physicians to be qualified as specialists by the boards. This is particularly true of surgery. If, as pointed out above, the medical schools are limited in the number of men they can train with their clinical facilities and if clinical facilities are available in the non-medical-school hospitals, it is logical to correlate the two so that the specialists that are needed may be trained.

extravagant, that it represents in all instances full value received and that discrepancies in operative costs in various hospitals represent the difference in care demanded by the complexity of the cases treated

The last problem deals with legislation. Voluntary hospitals should be concerned with the growing tendency of legislatures, including Congress, to consider hospitals in the same category as business and to include them in laws passed primarily to control industry. Hospitals should conform to many regulations, such as fire, building and sanitary laws, and should operate in many ways on business principles. But the demands of sickness, the conception of charity and the application of medical ethics make the operation of a hospital something more than a business.

One cannot operate on strictly business principles when one deliberately gives away something at less than cost. Legislation and regulations affecting hospitals should take this into consideration and should be separated from those regulating industry. Hospitals cannot survive a legislative program that, on the one hand, through the Minimum Wage Com-

mission, increases wages and reduces hours of labor, and on the other, by statute or departmental regulations, prohibits governmental agencies from paying full costs for the care of their beneficiaries. Legislation that affects hospitals should be patterned for hospitals, not for industry.

* * *

What has been said at length can be summed up in a few words. The health and death rates of a community are in direct relation to the amount of money intelligently spent on sanitation, preventive medicine, the education of doctors and others engaged in the care of the sick and the support of medical schools and hospitals. If the people of Boston and the United States want good hospitals, they must pay for them. If they want voluntary hospitals, they must support them through individual gifts, through industrial donations, through the requirement that governmental agencies assume their obligations in full and through modification of legislation affecting them. Only in this way can the flower of our hospital system, the pacemaking voluntary hospital, be preserved.

THE POSSIBLE ROLE OF THE COMMUNITY HOSPITAL IN GRADUATE TRAINING IN SURGERY*

FRANK GLENN, M D †

NEW YORK CITY

AMERICAN medicine and surgery have made great strides since ether anesthesia was first employed in Boston a hundred years ago. Hospitals during this century have become more numerous and greatly improved, the present trend being toward caring for an ever-increasing proportion of the population. These hospitals have become one of the important institutions of almost every community throughout the country. The part that they will fulfill in the health of the Nation in the future, it seems, will be even greater. The possible role of the community hospital in surgical training is but one aspect of the question.

In presenting this subject for discussion, I shall elaborate briefly on the community hospital as a unit and on the distribution of hospitals over the country. The established standards of surgical training are reviewed, and the need for extending surgical training in the non-medical-center hospitals is stated. The possible role of the community hospital in this surgical training is based on the premise that better surgical care is desirable. A plan is suggested for surgical training in these hospitals that, it is believed, will contribute to that ultimate goal.

The term "community hospital" is an elastic one. It may include the small hospital of a few beds at one extreme and the large city hospital of a thousand beds or more at the other. The hospital under discussion, however, is one in a town of 10,000 to 20,000 population and provides hospital care for 40,000 to 80,000 people within a radius of several miles. Such a hospital ordinarily has from 150 to 400 beds. It is an institution of first importance to everyone in the community and is operated by a lay and professional board representative of the people. A significant section of any hospital is the surgical service. The surgical therapy accorded the patients depends on the training and experience of the surgeon. Surgeons of the community hospitals should have breadth and firmness of foundation in their training because their responsibilities are great.

For a hundred and fifty years in this country surgical training was for the most part informal and vague. Over the past five decades various patterns that one might follow to become a surgeon have evolved. In the last twenty years these have become more distinct, with the result that surgical training has been defined and standards established by the American College of Surgeons and the American Board of Surgery. The American College of Surgeons¹ requires that candidates for member-

*Presented at the New England Postgraduate Assembly, Boston, October 30, 1946.

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the non-medical-center institution, by co-operation, can contribute a great step in the evolution of American medicine. Together, they can provide for the medical-school graduate an opportunity to fulfill the requirements of such boards as he may wish to qualify for.

The direct plan of training will not only provide an opportunity to develop but also create a relation between the physicians in the local hospitals and in the medical centers. Those from the former may attend meetings in the latter, using their additional library facilities and being afforded a channel for seeking aid in solving their more difficult clinical problems. Furthermore, the members of the staffs of the medical centers might be drawn on to speak on subjects of special interest. In turn, there would also be opportunities for those who had basic instruction in the centers to extend their training in the local hospitals and at the same time to become acquainted with practice. For it is indeed a difficult step from work in a large hospital to the actual practice of surgery in a community.

There is a strong trend for federal and state governments to assume control of hospitals, particularly in the building and maintenance of new hospitals. This is, of course, the product of a philosophy of government that seeks to regiment more and more the activities of its citizens. It includes the limitation of incomes and a so-called "redistribution of wealth." We may not as individuals agree with this program, but we are confronted with the problems it presents to the medical profession. One of these problems is financing the cost of training in the specialties. As you are doubtless aware, one of the most recent and far-reaching legislations, the Hospital Survey and Construction Act, was passed by the Seventy-ninth Congress of the United States and signed by the President during the early part of August, 1946.⁷ The stated purpose of the act is to assist the states as follows:

to inventory the existing hospitals, to survey the need for construction of hospitals, and to develop programs for construction of such public and other non-profit hospitals as will, in conjunction with existing facilities, afford the necessary physical facilities for furnishing adequate hospital, clinic, and similar services to all their people, and to construct public and other non-profit hospitals in accordance with such programs.

The emphasis in the building of the community hospitals has been on the physical plant and equipment. This is important, but more important is the hospital staff, which must be continually improved. The quality of the work done by a staff is dependent on the training of its members. At present, in many hospitals throughout the country, the surgery is done by men who were trained the hard way — by having a minimal amount of formal instruction. This method has produced many good surgeons and many poor ones. The community needs to contribute to the cost of the staff as well as to the building and its equipment. There is needed

a subsidy for paying certain members of the senior staff for carrying out a training program, in addition to providing the surgeon in training a sufficient income so that he can maintain a social position equal to that of his peers in other professions, such as law and engineering.

He who embarks on a career of surgery is confronted with a long period of training after graduation from medical school. Heretofore, the surgeon after an equally long period of residency or apprenticeship with little or no income could expect and have over a short earning period compensation that would enable him to equal the income of his medical confreres by the time he had reached the age when he could no longer work. Thus, his family, although often an addition of his later life, had security and provision for education. Today, taxes and the trend of fees make the annual net income of the surgeon during his most active periods of practice so limited that he cannot set aside an appreciable saving that will compensate for the long lean years of preparation or provide for his old age. If medical-school graduates are to continue to embark on surgical careers with an eye to their immediate and future livelihood, they should receive a reasonable subsidy during this training period. The cost should be borne by the hospital, the community or the state. If incomes are to be limited, a subsidy should be available when long years of preparation are required. Surgery, more than other divisions of medicine, demands intensive and prolonged training. The past generation has seen those who are now its leaders of surgery struggle through such training. The merit of the system for a few is undeniable, but for the majority its applicability is questionable. Is it not time to initiate a plan that will serve a greater number?

The various insurance schemes for hospitalization have gained great popularity over the past few years, and the trend continues. These programs, in a period of economic prosperity, have been accompanied by a decrease in the number of patients seeking free beds. Many private hospitals dependent on endowment for support have had a reduction in income and an increase in operational expense. These hospitals have had to embrace the insurance plans so far as hospital care is concerned. Ward services have been curtailed, and clinical material for training purposes has been reduced. This is unfortunate because patients properly utilized are benefited when used for teaching purposes. The community hospital properly staffed could, it seems to me, evolve a plan whereby patients would be cared for by the senior and resident staff as they are in the larger teaching centers. Once the system is established in a community and the work is well done, it will have the support of those who use the hospital.

Surgeons of the community hospitals, as well as other members of the medical profession, need no

The graduate training of the medical profession should be considered an important function of the medical schools, and indeed for the past fifty years in the United States they have become increasingly more active in this endeavor. With the requirements so clearly set forth by the various boards, it appears that the medical schools should interest themselves in the graduate training not only in their own hospitals but also in the hospitals within their community or sphere of influence. In some sections of the country, such as Boston and New York, there are several medical schools within a small geographical area. Would it not be a progressive step to enlist the aid of a medical school for a certain number of hospitals or for hospitals within a certain area? When I say aid, I do not mean that they would assume any control over the institution but rather that they would co-operate with the hospitals in the training of young doctors. These hospitals would request the medical school to review their facilities, to advise them on the problems presented by the training.

The medical school would offer the hospitals facilities for training or instruction in the basic sciences as required by the boards, staff members to participate in medical meetings held in the non-medical-school hospitals, a supply of partially trained young men and a stimulus for keeping abreast of current advances. The hospitals would provide the medical-school centers with additional opportunities for the men they had partially trained.

If full use were made of community hospitals with capacities of 150 beds or more whose annual admissions total 5000 to 6000 and over, there would be no lack of positions for training surgeons. A hospital of this capacity and larger that has been built, equipped and staffed to meet the basic requirements of the American College of Surgeons should lend itself to this purpose. I inquired directly of Dr. George H. Miller, director of educational activities of the American College of Surgeons, why these hospitals have not participated more in surgical training. His reply was as follows:

The expression "community hospital" is used with reference to such a wide variety of hospitals that it is a little difficult to discuss it accurately with reference to graduate training. However, I might say that as we are accustomed to think of community hospitals, one of the major obstacles to their participation in graduate training, even in the case of those which are large enough to offer considerable clinical material, is their apparent inability to develop properly organized departments which will place responsibility for the quality of the work done within the department on a recognized department head or chief. They tend to set up a paper organization in which the department headship rotates more or less by courtesy annually, and the members of the staff do not think of the head of the department as having any real responsibility, and sometimes would actually resent any suggestion that the chief was responsible for the quality of any work other than his own. This, of course, does not make a situation in which we can approve the placing of a good resident for training. Many of them also lack in the staff men who have kept up with the recent scientific developments in surgery sufficiently to let them hold a departmental conference and discuss usefully the basic science

interpretation of the clinical problems with which they are dealing.

We are very much interested in encouraging the bringing of such hospitals as far as possible into the sphere of influence of the medical schools through affiliation or collaboration. However, the local problems, except for a few choice endowed community hospitals or strong suburban hospitals near a metropolitan area, prevent the inclusion of many hospitals, which, on the basis of their bed capacity and clinical material, would seem to offer opportunity for graduate training experience.

For hospitals that are large enough and have the facilities to participate in graduate training a general plan is needed. I should favor the division of the clinical work into the four sections of medicine, obstetrics, pediatrics and surgery, each headed by a clinical head on a part-time basis. The hospital of this type requires a full-time pathologist and radiologist. The surgical service is but a part of the hospital, although an important one. The chief, or clinical director, should be well trained, progressive and interested in teaching. He would be the surgical director responsible for the surgery done in the hospital. He and his senior staff should receive pay for the time devoted to teaching the junior staff, which should be composed of residents or fellows. The teaching program should be comprehensive and well planned, with the assistance of the medical-center group. It should include regular ward rounds, staff conferences of the department and general hospital conferences in the form of clinicopathological conferences. All activities in the hospital should be open.

Thus, in these hospitals, men in training would have excellent guidance in diagnosis, preoperative therapy, surgical procedures and postoperative care by the senior staff men. On them would rest the task of correlation of operative data, gross and microscopic pathology and collateral reading or study. Clinical conferences and ward rounds are essential to improvement in the care of patients as well as in the instruction of the trainee. There are many large hospitals in the country that have competent and well trained men who take excellent care of patients but who contribute little or nothing to the instruction of those in training. This is particularly true in municipal, county and private hospitals located in towns and cities without medical schools.

In some cities the medical-school hospitals, long established, have trained the majority of the physicians in the community. The instruction received is reflected in their practice. They are influenced by what goes on in the hospital they were trained in. If they are on the staff of that hospital or a similar one, the influence is greater. This force for advance is lacking in communities far removed from medical schools. This situation, I maintain, can be changed. The medical schools can and should extend their sphere of influence. The materials for this rest in the hospitals that already exist and those that are being established. The medical-center hospital and

Incidence

The exact incidence of dysenteric arthritis is not known, either in the Theater as a whole or in the number of cases in which the diagnosis of bacillary dysentery was made. Arthritis has been encountered relatively often in some epidemics of dysentery and rarely or not at all in others.⁴ For example, a search of the records of the Twelfth General Hospital revealed 20 probable cases of dysenteric arthritis among 173 cases of proved or probable bacillary dysentery — an incidence of 11.6 per cent. At the Seventy-third Station Hospital, on the other hand, the diagnosis of bacillary dysentery was made in 1120 cases during 1943 and 1944, without the recognition of a single case associated with arthritis. Figures in the literature have similarly varied from less than 1 per cent to 5 per cent and over.⁴ Other hospitals in the Theater reported 21 cases of arthritis in association with bacillary dysentery, 10 of which showed conjunctivitis and urethritis in addition. The total number of cases was thus small, and the condition was chiefly confined to the Oran area. One can speculate also that, in a certain number of cases of acute arthritis, the association with dysentery was not recognized, since arthritis is known to occur in mild, easily overlooked cases of bacillary dysentery and even in the carrier state.⁵

Pathogenesis

That dysenteric arthritis is a metastatic infection, with organisms in and around the joints, has not been proved. In only a few recorded cases, in which cultures were taken in the field with opportunity for contamination, have dysentery bacilli been recovered from the synovial fluid.⁴ Since blood cultures have uniformly been negative, an allergic or toxic mechanism has been proposed, and animal experimentation has demonstrated the possibility of either. Finally, as pointed out below in the discussion of Reiter's syndrome, a secondary invader rather than the *Shigella* group may actually be responsible for the arthritis associated with bacillary dysentery.

Diagnosis and Clinical Features

The diagnosis of dysenteric arthritis was established only on a presumptive basis in the Theater, depending on the finding of an acute arthritis and a history of preceding dysentery. In a certain number of cases, stool cultures and agglutination reactions served as confirmatory tests. In the differential diagnosis, other forms of acute infectious arthritis, especially gonococcal, rheumatoid in an acute stage and gouty arthritis, as well as rheumatic fever, were considered.

In the clinical description that follows, since the arthritis was uniformly the disabling factor, no distinction is made between cases with or without urethritis and conjunctivitis. The interval between the first symptoms of dysentery and the development of arthritis varied between a coincidental onset and seven weeks, with an average of sixteen

and a half days. All the cases originated in the warmer months (June through October), the majority occurring in July and August. The arthritis usually arose acutely. Joints were severely inflamed, with effusion, and the course was severe and prolonged. Large joints, with the exception of the metatarsophalangeal, were involved oftener than small, the order of frequency being the knees (75 per cent of the cases), toes (especially the first metatarsophalangeal joint), ankles, shoulders, elbows and hands. In slightly over half the patients, there was bilateral involvement of at least one pair of corresponding joints. In common with other types of infectious arthritis, a few, rather than multiple, joints were affected, but monarticular arthritis was rare. In 9 out of the 20 cases, the arthritis was the only complication and was not accompanied by urethritis or conjunctivitis.

Ten patients also had urethritis which usually followed the onset of the arthritis, but occasionally preceded it. Seven of these had conjunctivitis in addition. The urethritis was usually mild and sometimes not even noted by the patient until he was questioned. In contrast to the arthritis, it cleared readily without specific treatment. No patients were encountered with involvement of other parts of the genitourinary tract, or with balanitis or penile ulceration, as described elsewhere.⁶ Ocular involvement, which occurred in 8 patients, consisted in a mild, bilateral, purulent conjunctivitis, with the exception of a patient with keratitis. All but one of these also had urethritis. The eye lesions cleared up readily, and no patient developed iritis, which was found in frequent association by Beiglböck.⁶

Laboratory findings were helpful only regarding cultures, agglutination tests and determinations of the sedimentation rate. The last was constantly elevated to a high degree during the acute stage of the arthritis, often reaching 100 mm in an hour (Westergren method). Stool cultures were positive in 4 of 17 cases, with organisms identified as *Shigella paradyserteriae* Y in 3 and *S. dysenteriae* in 1. Agglutination reactions to the *Shigella* group were positive in a titer ranging between 1:80 and 1:640 in 8 patients. In a total of 16 patients on whom both tests were done, 11 had either a positive culture or agglutination reaction, or both. Cultures of urethral and conjunctival discharges and of the joint fluid in 1 case were negative. X-ray examination of the affected joints showed only varying degrees of bony atrophy, without destruction, even after several months.

Treatment and Course

Several of the patients had received sulfadiazine or sulfaguanidine, with a favorable effect on the dysentery, but the subsequent development of arthritis was not prevented. Once the arthritis was established, the same drugs were tried unsuccessfully in 8 patients. That the arthritis tended to be

longer consider themselves isolated and in a position where their education cannot be continued. We have a comprehensive current medical literature, which should supplement an adequate medical library in the community hospital. And we have transportation facilities that should enable the profession to attend with ease county, state and even occasional national meetings where new material is presented. The radio and television, which have been used comparatively little for educational purposes of the medical profession, should be employed. Furthermore, by planning, staff members of the community hospital may have a few weeks every year or two during which they can engage in intensive study and observation of new methods as employed in the teaching centers. The United States today holds first place in medical progress, the medical profession, in one way or another, should be made aware of this fact, so that it may make the maximum use of the opportunity that exists. And, in particular, the opportunity should be most profitable for staff members of the community hospitals.

* * *

The development of surgery over the past hundred and sixty years in the United States has brought about the present standards established by the American College of Surgeons and the American Board of Surgery. These appear to be sound. If they can be adhered to, the quality of surgery in the future will be further improved. As indicated above, there are not enough positions in the hospitals that provide the facilities whereby these standards can be efficiently fulfilled. There are an adequate number of medical-school graduates each year who, after a year's internship, seek training in surgery, without success. If hospitals are to

be staffed with board members in surgery, the non-medical-center and community hospitals must equip themselves with the facilities that will enable them to participate in the training of the surgeons who are needed.

In effect, it is proposed that the community hospitals become teaching institutions, that they be the medical centers of the community and that they accomplish this with the advisory assistance and co-operation of a university medical center. Such a plan should materially increase the number of properly trained surgeons that will be needed in the future, what is believed to be of even greater importance is that it will stimulate the physicians associated with these hospitals to keep abreast of advances and create channels through which new information can be easily circulated. Benefits that may accrue from this will be of greatest value to the citizens of the community in which these hospitals function. This appears to be a progressive step in medical care, but it is not a step that can be taken without the whole-hearted co-operation of those who are involved. It requires liberal financing by the community and the support of the medical profession in both the community and the university medical center.

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REFERENCES

- 1 Graduate training in surgery: fundamental requirements for graduate training. *Bull Am Coll Surgeons* 30:383-394, 1945.
- 2 *Booklet of Information* 15 pp. Philadelphia: American Board of Surgery, June, 1945.
- 3 Johnson, V., Arestad, F. H., and Tipner, A. Medical education in United States and Canada. *J A M A* 131:1277-1354, 1946.
- 4 Arestad, F. H., and Westmoreland, M. G. Hospital service in United States. *J A M A* 130:1073-1161, 1946.
- 5 Report of Committee on Graduate Training. *Bull Am Coll Surgeons* 24:409, 1939.
- 6 Approved programs of graduate training in general surgery and in surgical specialties in hospitals of United States and Canada as of December 31, 1945. *Bull Am Coll Surgeons* 30:395-408, 1945.
- 7 Washington Letter. President approves hospital bill with reservations. *J A M A* 131:1429, 1946.

ARTHRITIS IN THE MEDITERRANEAN THEATER OF OPERATIONS*

III Clinical Description of Infectious and Other Types of Arthritis

LIEUTENANT COLONEL CHARLES L. SHORT, MC, AUS

IN ADDITION to the various types of joint disease described in the two previous papers,^{1,2} infectious and miscellaneous forms of arthritis were encountered among United States Army personnel in the Mediterranean Theater.

ARTHRITIS ASSOCIATED WITH BACILLARY DYSENTERY

The arthritis associated with bacillary dysentery, although infrequently diagnosed, seemed of particular interest on account of an unusual symptom-complex that was encountered, especially in the region of Oran, Algeria, in the warmer months of

1943. This syndrome, which consisted in arthritis with conjunctivitis or urethritis, or both, and which has been mentioned in reports in the literature, has already been described by Lieutenant Colonel R. H. Young,³ of the Twelfth General Hospital. A large part of the following material was thus derived from observations made at this hospital, although scattered reports of the type of arthritis under discussion, with or without this symptom-complex, were available from the records of other hospitals. Throughout this section, the term "dysenteric arthritis" is used purely for convenience, with the understanding that, as pointed out below, the *Shigella* infection may merely facilitate involvement of the joints and other structures by a secondary invader.

*The following material represents a condensation and a certain amount of revision of parts of a clinical monograph on arthritis prepared at the direction of the Surgeon, Mediterranean Theater of Operations, United States Army, and submitted to him in final form in June 1945.

activates or provides a portal of entry for the etiologic agent of Reiter's syndrome and that post-dysenteric arthritis is due to a secondary invader rather than to one of the *Shigella* group. This concept is supported by the facts that the organism causing bacillary dysentery has not been found in the joints in cases of arthritis associated with this disease, that the arthritis, unlike dysentery, does not respond to chemotherapy and that the histopathological findings in the case cited above with an acute arthritis following dysentery were typical of a severe case of Reiter's disease.

GNOCOCCAL ARTHRITIS

Incidence

Since the incidence of gonococcal arthritis in the Theater was difficult to determine, only a few representative samples and opinions are presented. A total of only 47 cases were reported by questionnaire from eleven general hospitals. This disease thus accounted for only a small part of the cases of arthritis seen in such installations. Similarly, low figures were estimated for station hospitals, even those handling a large number of patients with gonorrhea, the incidence being regarded as distinctly lower than that seen in the civilian population before the war. The proportion (2.5 per cent) of cases of gonococcal arthritis compared to the total number of patients with gonorrhea in the same general hospitals is surprisingly close to the civilian figure (2 or 3 per cent). This is explainable, of course, by the fact that the general-hospital admissions for gonorrhea were few and confined to cases resistant to therapy. In contrast, estimates as low as 0.2 per cent were received from hospitals primarily handling large numbers of gonorrheal patients.

In World War I a total of 7895 patients with gonococcal arthritis were admitted to United States Army hospitals — about 12 per cent of the arthritic patients, exclusive of those with rheumatic fever.¹² It seems highly likely that a much smaller number of cases were encountered in World War II. This difference was probably due to the specific therapy of gonorrhea with the sulfonamides and penicillin. A number of cases of arthritis occurred, however, after apparent penicillin cure of the urethritis, with an incidence in one station hospital of approximately 0.5 per cent.

Diagnosis

The diagnosis of gonococcal arthritis was made with great care in the Theater, in view of the regulations concerning line of duty and loss of pay that were in force until 1945. Although synovial-fluid cultures were not utilized as often as might seem desirable, the presence of gonorrhea was established bacteriologically, by culture if necessary in nearly every case so diagnosed. It was not generally recognized, however, that a patient might actually have rheumatoid arthritis that had been precipitated by a gonococcal infection of the genitourinary tract.

Such patients undoubtedly made up a number of those considered to have gonococcal arthritis resistant to specific therapy.

Treatment and Results

The treatment of gonococcal arthritis in the Theater was not carried out according to a uniform plan. Sulfonamides, which had been found nearly constantly efficacious in civilian practice, were discarded in favor of penicillin when this agent became available. A trial of penicillin, however, yielded uncertain results, even with a continuous dosage of 200,000 units daily for a week or more. The apparent failure of this method was probably more frequently due to confusion between gonococcal arthritis and rheumatoid arthritis precipitated by gonorrhea than to the existence of gonococcal strains resistant to penicillin in the dosage used. At the same time, conflicting reports on the efficacy of penicillin therapy in gonococcal arthritis appeared in the literature.¹⁴⁻²² In addition, although recent work has shown that an effective concentration in the synovial fluid is obtained with intramuscular penicillin,^{23,24} information to the contrary was available in the Theater.

From the considerations given above, sulfonamide therapy finally became the method of choice, with intra-articular penicillin in addition if possible. The largest series of cases encountered in the Theater was treated by Captain J. D. Phinney, who achieved the remarkably successful outcome of sending 28 out of 30 patients back to full duty. The patients were all given an initial dose of 3 gm. of sulfathiazole, followed by 1.5 gm. every six hours. Those with active gonorrhea or gonococcal conjunctivitis had in addition 200,000 to 400,000 units of penicillin intramuscularly at the rate of 25,000 units every three hours. If possible, an intra-articular injection of 10,000 to 25,000 units of penicillin was given daily for five or six days. One patient with bilateral ankle, knee and shoulder involvement received this treatment in each affected joint for nine days, with full recovery. Although synovial-fluid cultures were not performed, a large majority of patients in this series undoubtedly had gonococcal arthritis. In other reports of the use of a similar plan of treatment, the results were not uniformly favorable, again probably owing to a failure to recognize rheumatoid arthritis precipitated by gonorrhea.

Disposition

The dispositions in 47 cases collected from general hospitals were as follows: to duty, 17 (36 per cent), to limited service, 5 (11 per cent), and for evacuation, 25 (53 per cent). With the exception, then, of the series described above, the available results of treatment seem disappointing at first glance. In many of the cases that were considered failures, however, the patients were probably actually suffering from rheumatoid arthritis.

severe and persistent has been mentioned, but 3 cases were mild and the patients recovered within a few days to three weeks and were returned to duty. Three others were evacuated for other causes, although the arthritis had entirely cleared. The remaining 14 were sent to the Zone of the Interior, with the arthritis slowly but definitely improving in about half. The course of these patients approximated that described in the literature, except that an ankylosing type of dysenteric arthritis,⁴ with resultant permanent disability, was not seen.

Synovial Pathology

No reports on the pathologic histology of dysenteric arthritis have been discovered in the literature. One opportunity, however, presented itself to perform a synovial biopsy on a patient in the acute stage of an arthritis clinically compatible with this condition. The case history and pathologic findings were as follows:

A 31-year-old German prisoner of war was admitted to the Sixth General Hospital on May 29, 1945. He gave a history of an acute, febrile, at times bloody diarrhea from May 5 to May 27. A few days before the diarrhea had ceased, he had developed a painful swelling of the left knee and of the right 2 days later. Examination showed both knees to be moderately inflamed, with effusions—that on the left being more marked than that on the right. The temperature was 101.4°F on admission, falling to normal in 3 days.

Examination of the blood disclosed a hemoglobin of 13.8 gm per 100 cc and a white-cell count of 10,600, with 77 per cent neutrophils. Examination of the urine, a blood Kahn test and two stool cultures were negative. Aspiration of the left knee on June 1 revealed cloudy, yellowish fluid, containing 4425 leukocytes per cubic millimeter, with a differential count of 60 per cent polymorphonuclear cells, 38 per cent lymphocytes and 2 per cent monocytes. An electrocardiogram was normal.

The patient improved steadily, with no medication except large doses of sodium salicylate. On discharge on June 17, examination showed only slight synovial thickening of the left knee and on the right a small effusion and slight limitation in flexion.

About 1 week after the onset of the arthritis in the joint, synovial biopsy of the right knee was performed by Major Otto E. Aufranc. At operation a large amount of pale, yellow fluid with a soft white clot was evacuated. The synovial membrane was slightly pink and edematous, and the small vessels injected. There was no pannus.

Microscopical examination of the biopsied tissue was done by Major Sedgwick Mead, who reported as follows:

The tissue is edematous. Some of the blood vessels in the peritubular fat are ringed with round cells. The subsynovial vessels are dilated, and the cellular infiltrate is more pronounced in this layer. The synovial membrane itself is greatly thickened by the presence of a dense, homogeneous infiltration with large mononuclear cells, lymphocytes and, more rarely, polymorphonuclear cells. Occasional clumps of fibrin are seen, and the articular border is ragged, with nearly complete loss of synovial lining cells. Fibroblasts and new capillaries are growing in the synovial membrane.

Diagnosis: synovitis, acute, severe

Relation to Reiter's Syndrome

In 1916 Reiter,⁷ a German physician, reported the case of a patient with the triad of arthritis, conjunctivitis and urethritis. He believed that the condition was nongonococcal and due to a spirillum that he had isolated from the blood stream. A number of papers have subsequently appeared in the German and Scandinavian literature describing

a similar condition, but in no case has a spirillum been identified. The eponym, Reiter's disease, has persisted, although more descriptive terms have also been applied. Each author makes a distinction between this disease of unknown etiology and similar syndromes associated with gonorrhea and with bacillary dysentery. The first report on this subject in the English language⁸ appeared in 1942 and was followed by one on renal complications in 1944.⁹ All these cases were recognized at the Massachusetts General Hospital, where a series of 10 patients has now been collected. All the patients were men, usually young adults. The clinical manifestations, although often severe and including iritis and pyelonephritis, have thus far eventually cleared, with the exception of mild residual articular changes in certain cases. Recurrences, months to years later, however, have taken place. Extensive attempts to identify a bacterial or virus etiology have been unsuccessful. In February, 1945, Rosenblum¹⁰ reported 10 cases of Reiter's syndrome in personnel of the United States Navy, 5 of which arose in the South Pacific and 5 in the United States. In 2 cases recurrences took place, and one patient with severe involvement of the finger joints showed cartilage destruction on x-ray examination. Another had a widespread, acute skin eruption resembling erythema multiforme. No reference is made in the article to an association with bacillary dysentery. In the same year, 11 cases in the Army were recorded, with diarrhea as the first symptom or accompanying the arthritis in 4.¹¹

During the summer of 1944, of 2 patients with arthritis, conjunctivitis and urethritis admitted to the Sixth General Hospital, neither gave a history or evidence of dysentery or gonorrhea. One exhibited a shallow penile ulcer, which healed spontaneously after repeated negative dark-field examinations. This patient had received 800,000 units of penicillin without benefit. Another patient seen in August, 1943, was of especial interest. While awaiting evacuation for what seemed a typical infectious polyneuritis (Guillain-Barré syndrome), he developed urethritis, conjunctivitis and arthritis in rapid succession, without findings pointing toward dysentery or gonorrhea. In view of the reported incidence of polyneuritis,¹² presumably of toxic origin and secondary to bacillary dysentery, the possibility is raised of a common etiology for all the clinical manifestations of this patient.

A relation between the arthritis, urethritis and conjunctivitis following bacillary dysentery and Reiter's syndrome is immediately suggested from the essentially identical clinical pictures. It seems fair to assume that such an unusual symptom-complex probably arises from a single cause. Although, as pointed out above, Reiter's syndrome may be preceded by or associated with diarrhea, no evidence has yet been presented that an active or latent *Shigella* infection is responsible. A more logical explanation is that the dysentery merely

tism,³⁰ was diagnosed twice at the Three Hundredth General Hospital

SUGGESTIONS FOR IMPROVEMENT IN TREATMENT

Segregation of patients with arthritis in special hospitals or dispensaries is unnecessary in an overseas theater, but more efficient handling of such cases seems possible within the existing medical installations

Provision should be made in the forward areas for rapid examination and disposition of patients with articular symptoms to avoid the sending of large numbers to base hospitals. For officer personnel, an internist with interest in and some special knowledge of joint disease, an orthopedist and a psychiatrist should constitute a team. Laboratory requirements could be held at a minimum but x-ray examination would be necessary, especially in patients with back symptoms. Many of the patients with arthralgia or psychogenic rheumatism could thus be sent back to duty after a relatively short period of examination and treatment, and those with a real arthritis or doubtful cases evacuated to base hospitals

In general and station hospitals, one officer, preferably on the medical service, should be given the arthritic diseases as an assignment. Although he should be experienced and interested in arthritis, it would be his duty to perfect his knowledge of the subject in every way possible. He should see all cases of joint disease in consultation and thus constantly teach himself as well as the other ward officers. Cases of especial interest or difficulty could be transferred to his own wards. He should be responsible for the policies followed in the hospital for diagnosis, treatment and disposition of patients with arthritis and should personally handle such curable conditions as gonococcal arthritis. He should work in close co-operation with orthopedic and neuropsychiatric officers and with the laboratory and x-ray services. In this way, the problem of arthritis in fixed hospitals in an overseas theater could be handled to greater advantage, with a consequent reduction in hospitalization and manpower loss.

SUMMARY

Arthritis associated with bacillary dysentery was rarely diagnosed in the Theater, except in the Oran, Algeria, area during the summer of 1943. In many of these cases, urethritis and conjunctivitis were present, with a clinical picture closely resembling Reiter's syndrome. Evidence is presented that the Shigella infection merely facilitates involvement of the joints and other structures by a secondary invader.

The incidence of gonococcal arthritis was less than that found in prewar civilian practice, probably owing to early, specific treatment of gonorrhea.

Cases were recorded, however, after apparent cure of the urethritis with penicillin. The explanation of the unsatisfactory results of therapy probably lies in the failure to recognize rheumatoid arthritis precipitated by a gonococcal infection.

Suggestions are made for the more efficient handling of joint disease in an overseas theater.

REFERENCES

- Short C L. Arthritis in Mediterranean Theater of Operations. I. Incidence of joint disease — clinical description of rheumatoid arthritis. *New Eng J Med* 226:383-391 1947
- Idem. Arthritis in Mediterranean Theater of Operations. II. Clinical description of hypertrophic arthritis, arthralgia and psychogenic rheumatism. *New Eng J Med* 226:429-47 1947
- Young R H. Bacillary dysentery, conjunctivo-urethro-synovial complication. Read at Clinical Conference on Recent Advances of Medicine in Wartime November 6 1945 Oran, Algeria
- Strong R P. *Stutt's Diagnosis, Prevention and Treatment of Tropical Diseases*. Sixth edition. 2 vol. 871 pp. Philadelphia: Blakiston Company, 1942
- Manson's Tropical Diseases. *A manual of the diseases of warm climates*. Edited by P H Manson-Bahr. Eleventh edition. 1083 pp. Baltimore: William Wood & Company, 1940
- Beiglböck W. Zur Behandlung der Reiterischen Krankheit (Rheumatismus). *Deutsche med Wchnschr* 69:40, 1943
- Reiter H. Über eine bisher unerkannte Spirochäteninfektion (Spirochaetosis arthritica). *Deutsche med Wchnschr* 42:1535 1916
- Bauer W and Engleman E P. Syndrome of unknown etiology characterized by urethritis, conjunctivitis and arthritis (so-called Reiter's disease). *Tr A Am Physicians* 57:707-11 1942
- Colby F H. Renal complications of Reiter's disease. *J Urol* 52:415-419 1944
- Rosenblum H H. So-called Reiter's disease: triad of acute arthritis, conjunctivitis and urethritis. *U S Naval Med Bull* 44:375 1945
- Hollander J L, Fogarty C W Jr, Abrams N R, and Kydd D M. Arthritis resembling Reiter's syndrome: observations on twenty five cases. *J A M A* 129:593-594 1945
- Wilke G. Polyneuritiden nach chronischer Enterocolitis insbesondere nach Ruhr. *Deutsche med Wchnschr* 69:443 1945
- The Medical Department of the United States Army in the World War 1917-1929. Washington: Government Printing Office, 1921-1929
- Dawson M H and Hobbey G L. Clinical use of penicillin: observations in 100 cases. *J A M A* 1124:611-622, 1944
- Herrell W E, Nichols D R and Heilman D H. Penicillin: its usefulness, limitations, diffusion and detection with analysis of 150 cases in which it was employed. *J A M A* 125:1003-1011 1944
- Murphy R J. Experimental use of penicillin in treatment of sulfonamide-resistant gonorrhea. *Bull U S Army Med Dept* (No 79) 101-107 1944
- Sternberg T H and Turner T B. Treatment of sulfonamide-resistant gonorrhea with penicillin sodium: results in 1686 cases. *J A M A* 126:157-161 1944
- Scarcello A S. Penicillin in sulfonamide-resistant gonorrhea: review of 200 cases. *New Eng J Med* 231:602-612 1944
- Doolittle L H and Marshall H B. Penicillin treatment of sulfonamide-resistant gonorrhea. *J Urol* 53:634-637 1945
- Buckley T. Discussion of Doolittle and Marshall.¹⁹
- Reynolds L R and Werrauch H M. Use of penicillin in treatment of urogenital infections: clinical study of 69 gonococcal and 26 non gonococcal infections of urogenital tract. *J Urol* 53:614-629 1945
- Thompson G J. Clinical use of penicillin in genitourinary infections. *J A M A* 126:407-407 1944
- McAdam I W Jr, Duguid J P, Challinor W W and McCall A. Penicillin treatment of serous-cavity infections. *Lancet* 2:843-848 1945
- Balboni V G, Shapiro I M, and Kydd D M. Penetration of penicillin into joint fluid following intramuscular administration. *Am J Med Sci* 210:588-591 1945
- Fox M J and Gilbert J. Meningococcus infections with articular complications. *Am J Med Sci* 208:67-69 1944
- Strong P S, and Hollander I L. Complications of meningococcal infections: analysis of 100 cases. *Bull U S Army Med Dept* (No 78) 68-75 1944
- Appelbaum E and Nelson J. Sulfadiazine and its sodium compound in treatment of meningitis and meningococemia. *Am J Med Sci* 207:492-507 1944
- Rosenberg D H, and Arling P A. Penicillin in treatment of meningitis. *J A M A* 125:1011-1017 1944
- Reilly W A. Experiences with meningococemia. *Med Bull North African Theater Op* 2:85-87 1944
- Hench P S. Of recurring disease of joints (arthritis penarthritica parvum) apparently producing no articular residues. *J A M A* 115:2207 1940

MENINGOCOCCAL ARTHRITIS

Meningococcal arthritis was generally associated with meningococcal meningitis. Only 9 cases were encountered, the incidence of this complication being 5.3 per cent in 170 patients with meningitis in general hospitals. This figure is in general agreement with civilian and military experience in the United States.²⁵⁻²⁷ No essential difference was noted in the clinical features of the disease in these cases as compared with those observed in the United States or reported in the literature. Whereas the arthritis was occasionally found on admission, it was usually not recognized until four or five days had elapsed. The reasons for this apparent latent period are obscure. Early involvement of the joints probably takes place, but frank signs and symptoms of arthritis develop later or are not immediately noticed in an unresponsive patient in whom attention is directed toward the much more serious localization of the infection in the meninges.

As in the cases observed in the United States,^{26, 28} prior administration of the sulfonamides or penicillin neither prevented nor lessened the incidence of arthritis. Although mild, transitory involvement of multiple joints might come first, the process eventually settled in one or a few large joints, chiefly the knee. Inflammatory signs were variable, and some joints were acutely swollen and painful at the onset. Since serum was not used in the Theater, no question of serum sickness arose, and only a few synovial-fluid cultures were performed, with negative results. The course of the arthritis was not strikingly influenced by chemotherapy or penicillin, although intra-articular injections of the latter were not tried. Important points that were sometimes neglected in the management of knee cases consisted in the avoidance of fixation, the postponement of weight bearing until the inflammation cleared and the early use of quadriceps exercises. The severity of the arthritis varied, but most of the patients required four to six weeks' convalescence before function was fully restored. All were returned to full duty, with the exception of 1 patient with mild residual changes in the knees, who was sent to limited service.

Meningococcemia without meningitis was reported in 26 cases, with one evacuation hospital furnishing 5 cases.²⁹ This condition was often accompanied by pain in the region of the joints—sometimes caused by embolic skin lesions—and occasionally by a frank arthritis. The cases were often confused at first with rheumatic fever or erythema nodosum, the diagnosis usually being made finally on the basis of the typical picture,²⁹ although a few positive blood cultures were obtained. Cure and rapid return to full duty were accomplished in every case with the aid of chemotherapy, usually sulfadiazine.

GOUTY ARTHRITIS

This form of arthritis was carefully looked for in the hospitals in the theater, but only 15 cases

were reported. In World War I, a total of 82 such cases were admitted to Army hospitals.¹² In some cases in the Mediterranean Theater, the diagnosis was made on equivocal blood uric acid findings, without a characteristic clinical picture. A lack of colchicine prevented treatment of acute attacks and possibly, in certain cases, return to duty. Ten patients were considered unable to perform any sort of duty in the Theater and were evacuated. The remainder, chiefly officers with sedentary assignments, were able to resume their duties.

MISCELLANEOUS TYPES

Only 3 cases of tuberculous arthritis were reported from general hospitals in the Theater. The incidence in World War I was similarly low, a total of 188 patients being admitted to Army hospitals.¹³ In 2 cases, in which a knee and a hip were respectively involved, the diagnosis was obvious, but in another, a second biopsy of the ankle joint was required for an unquestioned diagnosis. All the patients were evacuated to the Zone of the Interior.

A diagnosis of undulant fever was made in 34 patients in general hospitals, a number of whom presented articular symptoms. None of these cases were confused with any type of arthritis except for one patient with multiple joint involvement, another with a suppurative knee requiring drainage and a third with osteitis of the spine.

Scarlet fever was rarely accompanied or followed by arthritis, but a few patients manifested a recrudescence of rheumatic fever, and two others a transitory arthritis.

A patient with a staphylococcal infection of the wrist of unknown origin, which was surgically drained, was the only one reported with a septic joint not associated with trauma.

Patients with certain infectious diseases presented themselves with skeletal aches and pains at the onset. Most conspicuous among such symptoms were the arthralgia occasionally noted in acute hepatitis, the severe pain and stiffness in the cervical region of sandfly fever and the exquisite tenderness resulting from the muscular localization in Weil's disease.

No case was observed in which arthritis could be attributed to amebic dysentery, malaria, granuloma inguinale or coccidioidomycosis. There were 3 cases of arthritis associated with lymphogranuloma venereum, but details were not available regarding the probable relation of the arthritis to this venereal disease. Acute disseminated lupus erythematosus, a rare disease and one that is much more frequent in women than in men, was diagnosed at least twice, but there were no articular symptoms that might have caused confusion. One patient with a joint condition resembling rheumatoid arthritis was suspected of but not proved to have periarteritis nodosa. The most recently described syndrome among the arthritides, palindromic rheuma-

urinary analyses, physical examinations, x-ray studies and blood Wassermann tests had been made. Of this group he studied in detail three sections — those with a family history of diabetes, those with a hereditary history of diabetes and those who had shown sugar in the urine. He writes, "What a wonderful work in preventive medicine it would be if

TABLE 1 Incidence of Diabetes

AGE	NATIONAL HEALTH SURVEY		GATE SURVEY		
	MALES	FEMALES	% OF SUBJECTS	%	per 1000
yr	per 1000	per 1000			
15-24	0.07	0.57	245	1	4.0
25-34	0.40	1.08	604	4	6.66
35-44	2.01	3.16	540	6	12.0
45-54	4.49	8.64	316	7	18.0
55-64	9.96	18.20	89	1	11.0
65 and over	14.58	21.47	7	1	120.0

we could identify all the persons having diabetes and potential cases of diabetes in the United States."

For diagnostic purposes Gate employed in blood sugar determinations the Myers-Bailey modification of the Lewis-Benedict method. Venous blood samples were used. The following is an account of Gate's findings.

The starvation blood sugar should be 0.14 per cent or more and the post-prandial should be 0.22 per cent. The blood sugar should not fall so low as the starvation sugar at the end of two hours, and there must be accompanying glycosuria.

We have classified potential cases of diabetes as follows: Those whose starvation blood sugars were under 140 milligrams, whose peak did not rise to 220 milligrams, whose two-hour blood sugar did not fall to 140 milligrams, but may have nearly approached it, and who have accompanying glycosuria. The higher limits of blood sugar have been used because the blood sugars usually run higher with this method of determination.

We have done glucose tolerance tests on 109 individuals. Seventy of these individuals had given a history of having some relative who had diabetes, 43 had shown sugar in the urine, and four had shown sugar in the urine and also had given a positive history.

Realizing that the glucose tolerance test may be inaccurate if the individual has been restricting his diet, no tests were done on persons who had been restricting their diet in any way. The glucose tolerance test, which we used, was as follows:

Each individual reported in the morning without breakfast and having had no food for approximately sixteen hours. A sample of venous blood was obtained and a specimen of urine, 100 grams of glucose in solution was given orally and samples of blood and urine were tested at one-half-hour, one-hour, two-hour, and three-hour intervals.

In Table 1 the incidence of diabetes found by Dr Gate is compared with that obtained by a house-to-house canvass conducted by the National Institute of Health.⁸ (A personal communication from Dr Gate disclosed that 159 of his 1800 subjects were females.) Instead of an average incidence of 1.200, as would be expected from the National Health Survey, Gate found a total of 20 diabetic patients, or 1.90.

Glucose-tolerance tests were performed in the 8 cases with a family history of diabetes, in 63 with a

hereditary history and in the 46 in which examination showed sugar in the urine. Eight patients were known to have diabetes, and in 8 with family histories of the disease the tests revealed no diabetes, 9 of the 63 with a hereditary history showed diabetes, and 11 of the 46 with sugar in the urine were so classified, but 8 of these had previously been known to have the disease. One case with a family history, 8 with a hereditary history and 10 with sugar in the urine, but without history, were classified as potential cases. Gate concluded that the incidence in this particular group was about twice what might be expected as compared with published estimates.

Gate observed a great deal of interest among the persons interviewed while this work was in progress. Many of those who had a familial history of diabetes or near relatives with diabetes had apparently been wondering whether or not they would develop the disease. Some had been assured by their physicians that they need not worry, others were extremely interested in having the glucose-tolerance test performed.

No difference in the incidence of diabetes was observed between subjects working in the office and laboratory and those who did varying types of operation and labor in the plant itself. The study concludes as follows:

Further investigation along similar lines in other groups even without glucose tolerance tests, but with random blood sugars, would yield very valuable information, and unquestionably would uncover many hitherto unrecognized diabetics.

The greatest benefit resulting from this investigation is not that we may have shown that the actual incidence of diabetes is higher than has been estimated previously. The real value is that we have found a number of individuals who did not know they had the disease and who now will be able to prolong their lives. Then, too, a goodly percentage of those who are potential cases may be able to avoid the disease because they have been forewarned of the danger.

DIABETES IN BERGEN

A notable article of the year is that by Hanssen,⁹ who was senior assistant in the medical department of the City Hospital of Bergen, Norway, between 1940 and 1943, having previously worked in Denmark under Hagedorn. His monograph includes a study of the morbidity, mortality, causes of death and complications of diabetes mellitus in Bergen from 1925 to 1941. The investigation was so thorough that no similar research of just this type is apt to be attempted soon, and in fact, I think that all of us should concentrate more and more on the study and care of present-day cases. The monograph not only covers data relating to the diabetic patients in Bergen but also includes the literature in both Europe and America, and in it will be found many valuable citations sometimes overlooked in this country.

Bergen's population was about 100,000, of whom 45 per cent were males. Since there is little migration of the inhabitants in Norway it was easy to trace the diabetic patients. There were few Jews

MEDICAL PROGRESS

DIABETES MELLITUS

ELLIOTT P JOSLIN, M D *

BOSTON

THE most notable achievement in diabetes mellitus during 1946 I consider to be the demonstration by Lukens and Dohan,¹ of the Cox Metabolic Unit, University of Philadelphia, of a fourth method by which the disease can be caused experimentally in animals. They accomplished this by the production of hyperglycemia in a cat for a period of two weeks. It will be remembered that Haist, Campbell and Best² showed that by the simultaneous administration of insulin, diabetes can be prevented in a dog receiving injections of anterior pituitary extract and that Lukens and Dohan^{3,4} prevented and "cured" the diabetes in a cat following injections of pituitary extract by overcoming the subsequent hyperglycemia and maintaining the blood sugar at a normal level by means of insulin, diet or phlorhizin. It is known that in animals in which a subtotal pancreatectomy has been performed, just as after injections of anterior pituitary extract, a period of hyperglycemia precedes hydropic degeneration. On the theory that if the prevention or lowering of hyperglycemia is useful its causation should be harmful, Lukens and Dohan, by intraperitoneal administration of glucose, induced hyperglycemia in cats, and after two weeks in an animal in which this condition prevailed they found diabetes accompanied by changes in the islands of Langerhans, including hydropic degeneration. Technically this is a notable achievement, as attested to me by Dr F M Allen, because of the difficulties generally encountered with experiments on this animal. Lukens and Dohan write as follows:

In summary, hydropic degeneration of the islands of Langerhans and permanent severe diabetes mellitus have followed the prolonged injection of intraperitoneal glucose-saline solution in normal as well as in partially depancreatized cats. Positive results were associated with prolonged hyperglycemia. These findings add further evidence in support of the hypothesis that a sustained elevation of blood glucose may, under certain conditions, lead to the production of damage to the islands of Langerhans in this species.

The importance of hyperglycemia in the etiology and treatment of diabetes is emphasized by Ricketts,⁵ of the University of Chicago, who marshals the evidence on this topic in so masterful a way that his study should be "must" reading for every medical student as an ideal presentation of the subject and for each doctor interested in diabetes because of its assembly of facts regarding the disease.

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Naturally, to those who believe heart and soul in the aggressive treatment of diabetes advocated by Naunyn, these papers are welcome. They fortify the thesis that control of the disease pays and confirm the opinions of Joslin et al,⁶ as well as helping to explain why the patients who closely follow this dictum are the ones freest of complications.

An example of such patients is afforded by a man (Case 2419) who developed the severe diabetes of childhood at the age of fourteen and a half years in 1920. For about ten years he had as skilled a diabetic nurse as I know. He meticulously followed the orthodox treatment of a low-carbohydrate, low-calorie diet, in addition to insulin and exercise, and the nurse even accompanied him when he piloted his own aeroplane on week-end trips. At twenty-six years of age he married a nondiabetic girl from a nondiabetic family, who in preparation spent nearly six months learning the principles of diabetes control in the house of the patient's mother. They now have three healthy children. A few months ago in a train wreck he sustained ten broken ribs, a punctured lung, a fourfold fracture of the scapula and a compound fracture of the wrist, and yet at the end of four weeks, on discharge from the hospital, he was told by his surgeon that his recovery had been as rapid as that of a nondiabetic person. The diet included 175-200 gm of carbohydrate, 60-75 gm of protein, 90-100 gm of fat, and 18 units of crystalline and 70 units of protamine zinc insulin daily.

Another patient (Case 2568) developed diabetes at the age of seven years and nine months. She followed a strict regime of fasting and was one of the first to take insulin in this country, under the supervision of Dr F M Allen. After twenty-five years of diabetes a third healthy baby was delivered—a triumph for the patient's courage and the combined skill of Drs Priscilla White, Raymond Titus and Warren Sisson.

STATISTICS

In 1942 Gate⁷ published a careful study, unfortunately overlooked, of a group of 1800 patients with examinations of the urine and blood with the purpose of identifying those who had diabetes or might develop it and of prolonging the lives of the former and possibly postponing or preventing the full development of the disease in the latter. For this survey Dr Gate utilized the employees of a large manufacturing concern on whom yearly

aminated. No relation was detected between the duration of the diabetes and the frequency of calcification or with high serum cholesterol figures (not less than 220 mg per 100 cc.) No great difference in the incidence of arteriosclerosis as shown by the roentgenogram was found between male diabetic patients over forty years of age (56 per cent) and nondiabetic patients with diseases of the heart, kidneys and blood vessels (67 per cent) or from another group without such diseases (50 per cent). For women the incidence was definitely higher in the first two

TABLE 3 Lesions Discovered at Autopsy in 429 Cases of Diabetes

LESION	CAUSE OF DEATH NO OF CASES	COMPLICATION NO OF CASES
Coronary sclerosis	6	177
Coronary occlusion with infarction	87	26
Myocardial failure	18	68

groups (37 and 33 per cent) than among those in the third and younger group (13 per cent). Therefore, the high frequency of arteriosclerosis on roentgenologic examination of diabetic patients demonstrated by Joslin and his associates is not confirmed.

Some of the patients with demonstrable arteriosclerosis showed signs of a defective arterial blood supply to the lower limbs, but no connection between these phenomena was demonstrable.* The reduction of the arterial blood supply to the lower limbs was first and foremost due to thickening of the intima that is not demonstrable on ordinary x-ray examination. This is also why the demonstration of such arteriosclerosis is of no special prognostic significance in any given case, diabetic or otherwise.

Among Hanssen's 292 diabetic patients whose deaths were due to known causes, the deaths from heart disease were attributed to arteriosclerosis and hypertonia in 15 per cent of the male and 16 per cent of the female patients. Among the 108 diabetic patients examined post mortem were 9 who died of heart disease, which in 5 cases consisted of infarct of the heart and in 4 of heart failure. In contrast, 44.5 per cent of cases in the Joslin series of 651 deaths, outside and in the hospital, from January 1, 1944, to May 15, 1946, were cardiac deaths,¹² but it should be pointed out that this series is at a distinctly later period. Among 429 deaths at autopsy at the George F. Baker Clinic, 111, or 26 per cent, were due to heart disease, the percentage having risen from 22 in 1940.¹⁶ Table 3 presents the types of lesion discovered at autopsy in the most recent Warren-Joslin group of 429 cases. Again, the longer duration of the diabetes, especially in patients dying

*The high percentage of arteriosclerosis in the legs of young diabetic patients in the Joslin group is believed to be due, first, to the low level of nutrition of these young people, who were treated just before or just after the discovery and use of insulin in 1922, secondly, to the low-carbohydrate and relatively high-fat diet in the period mentioned, and thirdly, and above all, to the exceptionally long duration of the diabetes in these youthful patients of whom we have had a relatively large number.

under fifty years of age, and the increasing age of these relatively young patients at death are considered factors that distinguish this group from those in the Norwegian study. Hanssen cites Wilder as emphasizing the great frequency of severe coronary sclerosis in female diabetic patients and refers to the paper of Root et al.¹⁷ in which the incidence of death from coronary occlusion among diabetic male patients was twice to four times as high as that among nondiabetic men of the same age group and four to ten times as high among diabetic as compared with nondiabetic women.

Cerebrovascular accidents, in contradistinction to cardiac disease, were more frequent (18.8 per cent) in the Bergen group than in either the 1946 series (9.4 per cent) or the 1944-1946 series (11.4 per cent) of Joslin. All data agree that the incidence of such accidents is much higher in female patients.

Although no cases of acute or chronic nephritis were observed by Hanssen, albuminuria was present in 5 per cent of the men and 7 per cent of the women over fifty years of age. The difference between these data, which represent a former epoch, and those in our experience with children with diabetes of long duration is expressed by Dr. Priscilla White,¹⁸ who states that between 1940 and 1946 nephritis had become the chief cause of death in patients with the onset of diabetes in childhood. In 84 cases of childhood diabetes of more than ten years' duration, 31 patients died of nephritis. Premature development of arteriosclerosis is already yielding to better dietary and insulin treatment. Under forty years of age, severe grades of intercapillary glomerulosclerosis were found in 13 of 40 cases at post-mortem examination.¹⁹

Gangrene was responsible for 11 of 125 deaths in the Bergen City Hospital. Amputations were far more numerous in the Oslo City Hospital than in the Riks Hospital in Oslo. In the Joslin series, the incidence of deaths from gangrene in 651 cases from 1944 to 1946 was 2.9 per cent, — a decrease from 4.4 per cent in the earlier series — but in the series of cases at autopsy the incidence was 12 per cent, as compared with 13 per cent in the earlier group. A percentage increase in the deaths from gangrene would not have been surprising, because of the growing number and relatively higher percentage of such cases in patients admitted to the George F. Baker Clinic, despite the lowering of surgical mortality. Hanssen calls attention to the frequency of gangrene in female patients.

For comparison two analyses (Tables 4 and 5) are given that demonstrate, respectively, the effect of the duration of diabetes on the mortality in cases in which the patients died of arteriosclerosis and coma and the changing sites of arteriosclerosis at successive periods. These tables are based on Tables 58 and 60 in the study of Joslin et al.,⁶ which had not appeared when Hanssen's article was written.

In general, the diet was low in calories and carbohydrate but relatively high in fats. Insulin was used in moderate amounts, being available for all and protamine zinc insulin having been employed since 1936. There were 392 deaths from diabetes between 1925 and 1941 and 402 known living diabetic patients in October, 1941, making a total of 794 cases. These figures were obtained from death certificates, cases treated in the City Hospital, patients listed for supplementary food rations and the complete replies received from questionnaires sent to physicians.

Particular attention was paid to arteriosclerosis, examination of the heart, the vessels in the right leg and the eyes, as well as electrocardiograms, being utilized.

The ratio of the 402 diabetic patients to the general population in Bergen in 1941 was 3.2 per 1000 males and 4.3 per 1000 females, the average being 3.8 per 1000, of whom 43 per cent received insulin. For a comparison, in Oslo the incidence — on the basis of patients receiving supplementary rations on July 1, 1943 — was 4.3 per 1000, of whom 54 per cent were receiving insulin. The author cites Falta as giving the incidence of diabetic patients in Vienna in 1940 as 5 per 1000 population.

The age at onset of the disease is placed at a decade later in life (sixty to sixty-four years) in Bergen than in the United States. Of the total of 794 cases there were only 29 with onset under the age of fifteen years, or about half the percentage in the Joslin series.

Just as Lombard and Joslin¹⁰ noted the unreliability of computing morbidity rates from mortality figures, Lundberg, cited by Hanssen, wrote in 1938, "It is probable the time will soon come when it will be quite impossible to employ the mortality figures for estimating the frequency of diabetes in the population." As a matter of fact, in Bergen from 1925 to 1941, only 58 per cent of the male and 68 per cent of the female diabetic patients were registered as having died of the disease. These figures are similar to those of 62.9 and 64.3 per cent for Massachusetts in 1936 and 1946 found by Lombard and Joslin and that of 69.4 per cent observed by Palmer¹¹ in Seattle.

Of the 392 deaths in Hanssen's study, 125 occurred in the City Hospital, and of these, 108 cases were autopsied. Table 2 presents the causes of death in the Joslin¹² group of cases as compared with those in the Hanssen monograph.

The treatment of diabetic coma in Hanssen's group was similar to that employed in the George F. Baker Clinic, glucose and alkalies being omitted. The predominant cause of the high case mortality was the delay of treatment.

Under fifty years of age hypertonia was exceptional. Above that age both systolic and diastolic hypertonias were frequent, 43 per cent of the male and 68 per cent of the female patients with blood

pressures of over 160 systolic, 100 diastolic, as compared with 25 per cent of the normal men and 36 per cent of the normal women of the same age group. Blood pressures over 201 systolic, 121 diastolic, were observed in 10 per cent of male and 23 per cent of female patients. Hanssen notes that elderly people tend to have a high systolic but not a high diastolic

TABLE 2 Causes of Death among Diabetic Patients in the Series of Hanssen⁹ and Joslin¹²

CAUSE OF DEATH*	HANSEN SERIES		JOSLIN SERIES	
	(1922-1936)	(1925-1941)	(1937-1943)	(1944-1946)
	PERCENTAGE	PERCENTAGE	PERCENTAGE	PERCENTAGE
Diabetic coma	8.4	8.2	3.4	3.1
Arteriosclerosis	53.8	48.0	64.0	66.6
Infection	13.6	22.0	11.5	7.8
Tuberculosis	4.2	4.1	2.6	2.5
Cancer	8.8	8.6	8.8	8.9

*There were 392 deaths in Hanssen's series. In the Joslin series the total deaths were, respectively, 2583 and 651 in the periods 1937-1943 and 1941-1946.

pressure. He observed that diabetic retinitis was particularly frequent in diabetic women.

Arteriosclerosis was observed more frequently at autopsy in the Bergen series than in that of Warren¹³ presumably because 84.5 per cent of patients in the former were over fifty years of age in contrast to 67.5 per cent of those in the latter. On the other hand, coronary occlusion occurred in only 6 per cent of cases in the Bergen series, in contrast to 20 per cent in that of Warren. The heart weights were greater in the Bergen series, but the patients were older and comparative body weights were unknown.

Comparisons of the incidence of arteriosclerosis in different communities are open to serious criticism, and Hanssen cites Björnsson's¹⁴ observations regarding this problem in Iceland, Copenhagen and Vienna. Local factors, sex, occupation, environment (town or country) and peculiar or different hospital conditions may have been of great significance. General impressions, unsupported by an actual analysis of available material, are not conclusive, clinical investigations are not sufficiently accurate, and even pathological and anatomical data really depend on the subjectivity of the pathologist.

Roentgenologic examinations of the arteries of the leg were carried out on 451 diabetic patients in a search for calcification. Calcification was rare under the age of forty years but increased with the patient's age, being found above forty years of age in 56 per cent of the men and in only 37 per cent of the women in the same age group despite the greater frequency of systolic and diastolic hypertonia in the female patients. Extensive calcification, however, was more frequent among female diabetic patients than among the nondiabetic women ex-

*Studies of the pelvic arteries were not made. During the last five years Dr. Priscilla White¹⁵ has found that when the pelvic arteries are visualized in a pregnant woman the prognosis for a living child is definitely less favorable than otherwise. Thus many of these patients abort and only 20 per cent have had a living child regardless of whether or not they are treated with hormones. Dr. White considers a ray examination of the pelvic arteries to be of the greatest importance.

practice is essential to furnish the rapidly growing number of diabetic patients the treatment they need

To live successfully with diabetes one must know the rules, and to teach these to patients is the function of the physician. In the first place, this demands more time than the doctor has at his disposal, and in the second place, it would cost the patient too much. Therefore, the doctor must get someone to do the elementary teaching for him — his wife, his child, his nurse, his secretary, his technician or another patient whom he has helped. The doctor must utilize the services of someone else, but that is not the whole of the story. At stated intervals he should assemble his patients, young and old and those with diabetes of long and short duration, and conduct a class for an hour or so. This will obviously cost the patient less than the \$8.00 a day, in addition to laboratory fees, in a ward bed in a hospital, in addition, the physician will receive his return, because he will constantly be building up a group of patients who come back out of necessity for regulation or follow-up over a period more than three times as long as formerly.

The Clinitest apparatus,* although by no means perfect, simplifies the treatment of the patient enormously, and I believe that before long a simplified blood sugar test will be available. A better use of neighborhood laboratories should be made. The diabetic patients themselves should be encouraged by small contributions to bring the laboratories up to date as a protection in times of emergency.

THE CHANGING TYPE OF HOSPITAL PATIENTS

The type of diabetic patients treated in hospital wards has greatly altered, and our experience is doubtless only an epitome of that of others. In 1941 the average duration of the diabetes of the patients in our group treated at the New England Deaconess Hospital was seven years and one month. Recently, a survey revealed that patients at the same hospital had already had the disease on the average well up toward thirteen years or almost within a year of the average duration of life in all the fatal cases in the Best Era. Only 1 in 10 could attend the diabetic classes held in the adjoining George F. Baker Building, and only a few weeks later a similar survey of 34 patients showed that only 1 in 7 could attend class. For every three years since the discovery of insulin the duration of life of diabetic patients, on the basis of our fatal cases, has risen one year, it is evident that the backlog of old and crippled diabetic patients will increase and thus fill hospital beds. And the tragedy is that these patients, who have fought the disease for years and whom we respect and are glad to help, are seldom likely again to be self-supporting. Yet each of them by a prolonged stay will bar from entrance a multitude of

young patients fully capable of being taught in a brief time to be efficient for years. This is why the family doctor must enter into the picture far more than ever before. It is he who can protect these thousands of diabetic patients. Contrary to many, I believe that, because of things like this, the future will, or at least can, bring the family doctor into his rightful and important place in medicine.

PREGNANCY IN DIABETES

The obstetric series of White, Titus and Sisson continues to expand. It is to be hoped that similar reports of a similar class of diabetic patients — namely, those of considerable severity and long duration — will appear for comparison. Summaries for 271 cases are presented by Joslin et al.,⁶ and the data in 23 cases of diabetes of twenty or more years' duration will be published in the March, 1947, issue of the *Medical Clinics of North America*.

The principles underlying their methods consist primarily in meticulous care of the patient with the realization that renal glycosuria is a major factor in pregnancy and that one must provide for sufficient calories to be utilized by the mother and the fetus, at the same time, with the multiple doses of insulin often required, the patient must be protected against hyperglycemia.

Toxemia of pregnancy, they believe, can be anticipated and often controlled by hormonal changes, its appearance in the latter months of pregnancy is always accompanied by albuminuria, a rising blood pressure and a gain in weight. Irrespective of these possibilities, delivery is usually favored in the thirty-seventh or thirty-eighth week by cesarean section. The healthy-appearing baby, however, should receive the attention given to a premature infant. Careful drainage, suction and oxygen and an incubator are indicated. The infant should receive no food or drink for one to three days. Obviously, the management of pregnancy in a mature multipara with slight, or even temporary, glycosuria, does not require such drastic measures.

In the presence of a rising serum chorionic gonadotropin level, diethylstilbestrol is injected daily and in increasing doses, and conversely when the urinary pregnanediol is falling, Proluton is administered daily. Even though the pregnancy is uncomplicated I gather that Dr. Titus prefers to deliver the hormonally treated patient rather than one who has not received such medication.

The latest results are 330 deliveries since January 1, 1936, with a single maternal death from hepatitis, as shown by autopsy, six weeks after delivery. The survival of infants prior to 1936 was approximately 50 per cent. In the present series, the survival rate in 61 cases of complicated pregnancy in which the mothers were not treated was 46 per cent, that in 198 complicated cases treated with hormones was 90 per cent and that in 71 uncomplicated cases, in

*Manufactured by Ames Company Incorporated, Elkhart, Indiana.

Hanssen noted the rapid disappearance of large livers in young diabetic patients following the more adequate treatment and control of the diabetes that the introduction of protamine zinc insulin made possible, an observation also made by White et al.²⁰ Acute hepatitis and hemochromatosis were not encountered. Gallstones were no more frequent among male diabetic patients than among the controls, but

Discrepancies between the official data of mortality and the true facts of diabetic patients dying with the disease but not of it are readily explained. Before 1914 approximately two thirds (63.8 per cent) of all diabetic patients here and abroad died of diabetic coma, an easily recognized and recorded diabetic death. Today, only 3.1 per cent of diabetic patients in our group die of coma. Approximately

TABLE 4 Influence of Duration of Diabetes on Mortality in Patients Dying of Arteriosclerosis and Diabetic Coma⁶

PERIOD	AVERAGE DURATION OF DIABETES*	TOTAL NO OF DEATHS	DEATHS FROM COMA	DEATHS FROM ARTERIOSCLEROSIS	AVERAGE AGE AT DEATH
	yr		%	%	yr
1898 to June, 1914 (Naunyn)	4.9	326	64	17	44.5
June, 1914, to August 1922 (Allen)	6.1	836	42	24	46.7
August, 1922, to December 1925 (Banting)	7.5	537	21	41	54.3
January, 1926 to December 1929 (Banting)	8.4	918	11	49	60.0
January, 1930, to December, 1934 (Banting)	10.0	1741	5	58	62.7
January 1935, to December, 1936 (Banting)	11.6	793	4	59	63.9
January, 1937, to December 1939 (Hagendorn)	12.4	1229	4	62	64.8
January, 1940, to December 1943 (Hagendorn)	13.3	1354	3	66	65.0
January, 1944 through May 15, 1946 (Best)	14.1	651	3	67	64.5

*Based on cases of known duration

they were encountered oftener in female diabetic patients. There were 2 cases of cancer of the pancreas, but none of acute necrosis of the pancreas or of pancreatic calculi. The morbidity and mortality from tuberculosis were not of any great importance, — 4.1 per cent, — in contrast to the high incidence

9 per cent die of cancer, instead of 1.5 per cent as heretofore, diabetes thus losing precedence in statistical enumeration, 67.4 per cent died of cardiorenal vascular complications in the period since 1944, as compared with 17.5 per cent in that from 1898-1914. These and other facts regarding the causes of death

TABLE 5 Site of Terminal Lesion in 4495 Diabetic Patients Dying of Arteriosclerosis⁶

PERIOD	TOTAL NO OF DEATHS*	SITE OF ARTERIOSCLEROTIC LESION				
		BRAIN	KIDNEYS	HEART	PERIPHERAL VESSELS	UNDETERMINED
		%	%	%	%	%
1898 to June, 1914 (Naunyn)	57	18	18	35	21	9
June, 1914, to August 1922 (Allen)	203	22	15	40	17	6
August, 1922, to December, 1929 (Banting)	672	20	9	49	19	3
January, 1930 to December, 1936 (Banting)	1474	18	8	57	13	4
January, 1937 to December 1943 (Hagendorn)	1655	22	6	60	8	4
January 1944, to May 15, 1946 (Best)	434	22	7	64	4	3

*Tabulation by the Statistical Bureau of the Metropolitan Life Insurance Company

of the disease among diabetic patients in various European centers, notably Paris and Vienna.

What is really needed for a better understanding of both the incidence and the clinical features of diabetes is a survey of isolated localities all over the world, such as that now in progress in Oxford, Massachusetts, a town of 5000 inhabitants. Such surveys will give a true idea of the morbidity of the disease. For a knowledge of the mortality one must depend more and more on private statistics from private clinics and groups of physicians particularly interested in the disease who follow up all their cases, here again discrimination in the evaluation is necessary on account of varying local conditions

of 8384 diabetic patients in our series, as well as data from various international compilations, have recently been summarized.¹²

MEDICAL TREATMENT

Hospital costs for diabetic patients are rising, but I am sure that all physicians appreciate the fact that the cost of medical care should be and, indeed, is decreasing. The reason is plain. Hitherto the diagnosis of diabetes was usually made among the well-to-do, but a lower economic stratum of society is receiving better medical care and these patients simply do not have the money to pay for the services formerly rendered. A reorganization of medical

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M.D., *Editor*

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CASE 33131

PRESENTATION OF CASE

A fifty-four-year-old Irish retired elevated-rail-road employee was admitted because of shortness of breath.

For the previous ten to fifteen years he had had attacks of asthma occurring at night during which he was short of breath and coughed. He was usually somewhat relieved when he brought up phlegm, which was white and thick, and he was able to breathe much better sitting up. When he had such attacks he usually spent the rest of the night in a chair and was over the attack by morning. A physician gave him "pills" for the asthma. The attacks had recently increased in frequency. For the preceding two years the patient had noted shortness of breath on exertion, particularly during the day, and the ankles had begun to swell. He was given digitalis, which he had taken irregularly ever since. The salt intake had been reduced. An electrocardiogram a year before admission had revealed auricular fibrillation (Fig 1). On fluoroscopy the heart was moderately enlarged, and there was a prominent pulmonary artery and questionable enlargement of the left auricle. The heart sounds were distant, and no murmurs were heard. During the year the symptoms had become progressively worse, with occasional remissions, and the patient was forced to quit work. For three months before admission he had been unable to negotiate three flights of stairs. The legs swelled progressively up to the thighs, and the abdomen had become swollen. He had taken some digitalis for a few days before admission. His physician had given him mercurial diuretics.

The patient remembered having had "rheumatic fever" at the age of seventeen, when he had been kept in bed with swollen joints and had felt quite sick for about six weeks, but he knew of no heart murmur and had subsequently had no swollen joints, nosebleeds, chest or abdominal pain. He had never had high blood pressure. Up to two years before admission he had drunk one or two glasses of beer and half a pint of whiskey a day, but this had been almost entirely omitted since then.

Physical examination revealed a florid, extremely cyanotic, obese, well developed man with signs of weight loss in the face and upper extremities. He was partially sitting up in bed and breathing with moderate difficulty and with audible coarse wheezing. There was questionable icterus in the scleras. The fundi showed mild arteriosclerotic changes. There was a moderate rhinophyma. The neck

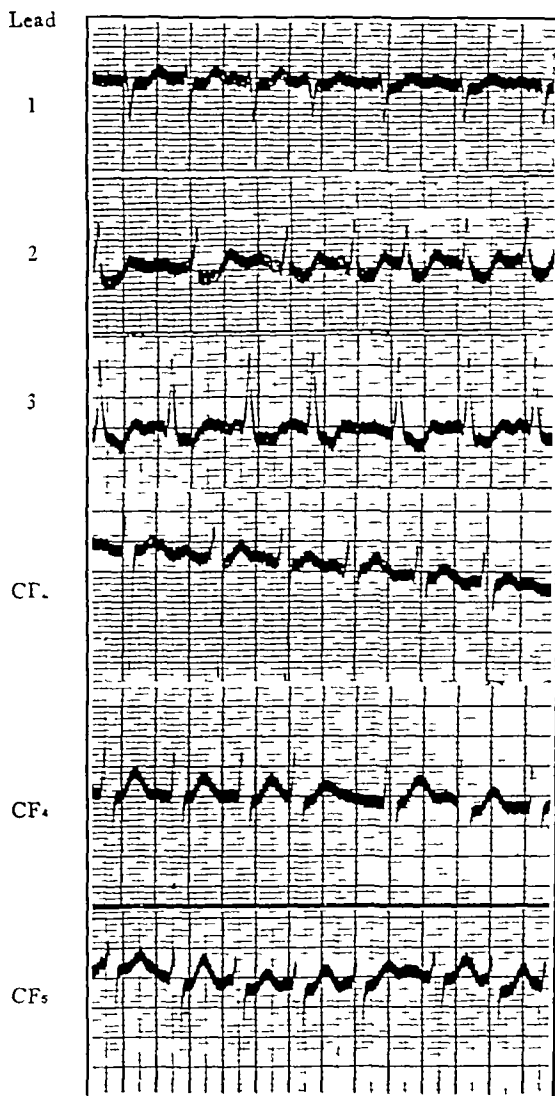


FIGURE 1

veins were full but not pulsating. The heart was enlarged to the left, reaching the anterior axillary line, with a forceful apical beat in the fifth inter-space. The rhythm was irregular and alternated between bigeminy and trigeminy with an apical

which the mothers were not treated with hormones, was 97 per cent

SURGERY

Reference is made to a recent article by McKittrick²¹ in which advances in the surgical treatment of complications of diabetes have been set forth. Suffice it to say that, whereas in the period 1923-1941 the mortality for amputations through or above the mid-lower leg was 14.1 per cent in 609 cases, in 1942-1945 it had dropped to 4.7 per cent in 212 cases, and that for major and minor amputations it had similarly dropped from 9.7 per cent in 1036 cases in 1923-1941 to 2.6 per cent in 229 cases in 1944 and 1945. This is undoubtedly due in large measure to the use of the sulfonamides and penicillin. But technically there has been a distinct improvement in procedures for saving the feet. In the past, following the removal of a gangrenous or osteomyelitic toe, the diabetic patient returned after an interval for the amputation of another or even a far higher amputation. To overcome this Dr McKittrick has introduced a transmetatarsal type of operation by which all the toes are removed at one time, and by the use of a long plantar flap, a useful foot is obtained. The first operation was performed in March, 1944, and by May, 1946, it had been done in 75 cases. Of these, 11 were failures, largely because operations have been undertaken in more and more serious and complicated cases to learn the limitations of this type of surgery. Staphylococci were cultured from the wounds in 52 of the 75 cases, either in pure culture or in combination with other organisms.

MISCELLANEOUS CONSIDERATIONS

Diabetic Camps and Societies

A list of diabetic camps and diabetic societies was given in last year's progress report.²² I am happy to say that in the future this listing will be continued and amplified by the American Diabetes Association.

Publications

Diabetes Abstracts, published by the American Diabetes Association, in conjunction with Eli Lilly and Company, continues to be invaluable. All are

looking forward with anticipation to the publication of the *Proceedings* of the meeting held in Toronto last September when the Association joined with the University of Toronto for the celebration of the discovery of insulin by Banting and Best.

Insurance

Insurance of diabetic patients is now a *fait accompli*. A new life-expectancy table to replace that of 1938 is in process of compilation by the Metropolitan Life Insurance Company and Joslin. This is in part subsidized by the Diabetic Fund of the Boston Safe Deposit and Trust Company and by gifts to it for this purpose from two insurance companies.

REFERENCES

- 1 Dohan F C, and Lukens F D W. Lesions of pancreatic islets produced in cats by administration of glucose. *Science* 105:183 1947.
- 2 Haist, R E, Campbell, J, and Best, C H. Prevention of diabetes. *New Eng J Med* 223:607-615 1940.
- 3 Lukens, F D W, and Dohan F C. Pituitary-diabetes in cat: recovery following insulin or dietary treatment. *Endocrinology* 30:175-202 1942.
- 4 Lukens, F D W, Dohan, F C, and Wolcott M W. Pituitary diabetes in cat: recovery following phlorhizin treatment. *Endocrinology* 32:475 487, 1943.
- 5 Ricketts, H T. Does hyperglycemia harm diabetic patient? *N Clin North America* (in press).
- 6 Joslin E P, Root H F, White P, Marble, A, and Bailey C. C. *The Treatment of Diabetes Mellitus*. Eighth edition. 861 pp. Philadelphia: Lea & Febiger 1946.
- 7 Gate E W. Diagnosis of undetected diabetes: report of study of group of 1800 individuals. *Indust Med* 11:387-391 1942.
- 8 National Institute of Health 1935-36. *The Magnitude of the Chronic Disease Problem in the United States*. Division of Public Health Methods. National Institute of Health. United States Public Health Service, Washington 1938.
- 9 Hansen P. *Diabetes Mellitus in Bergen 1925-41*. 179 pp. Oslo: Johan Grund Tanum, 1946.
- 10 Joslin E P, and Lombard H L. Diabetes epidemiology from death records. *New Eng J Med* 214:7-9, 1936. *Idem*. Unpublished data.
- 11 Joslin et al. 6: P 25.
- 12 Joslin et al. 6: P 229.
- 13 Joslin et al. 6: P 234.
- 14 Björnsen, J. *Arteriosclerosis: A clinical and statistical study*. 249 pp. Copenhagen: Einar Munksgaard 1941.
- 15 White, P. Personal communication.
- 16 Joslin, E P, Root, H F, White P, and Marble, A. *The Treatment of Diabetes Mellitus*. Seventh edition. 707 pp. Philadelphia: Lea & Febiger, 1941.
- 17 Root H F, Bland E F, Gordon W H, and White P D. Coronary atherosclerosis in diabetes mellitus: postmortem study. *J A M A* 113:27-30 1939.
- 18 Joslin et al. 6: P 768.
- 19 Joslin et al. 6: P 747.
- 20 White, P, Marble A, Bogan, I K, and Smith, R. M. Enlargement of liver in diabetic children. II. Effect of raw pancreas, betaine hydrochloride and protamine insulin. *Arch Int Med* 62:751-764 1938.
- 21 McKittrick, L. S. Recent advances in care of surgical complications of diabetes mellitus. *New Eng J Med* 235:929-932 1946.
- 22 Joslin E. P. Diabetes mellitus. *New Eng J Med* 234:476-482 1946.

under consideration. Perhaps Dr King will tell us about that later. Asthma at night may be a different kind of condition, but as I understand it, bronchial asthma can bother patients mostly at night.

Was the shortness of breath on exertion a sequel to the story of asthma such as we frequently see?

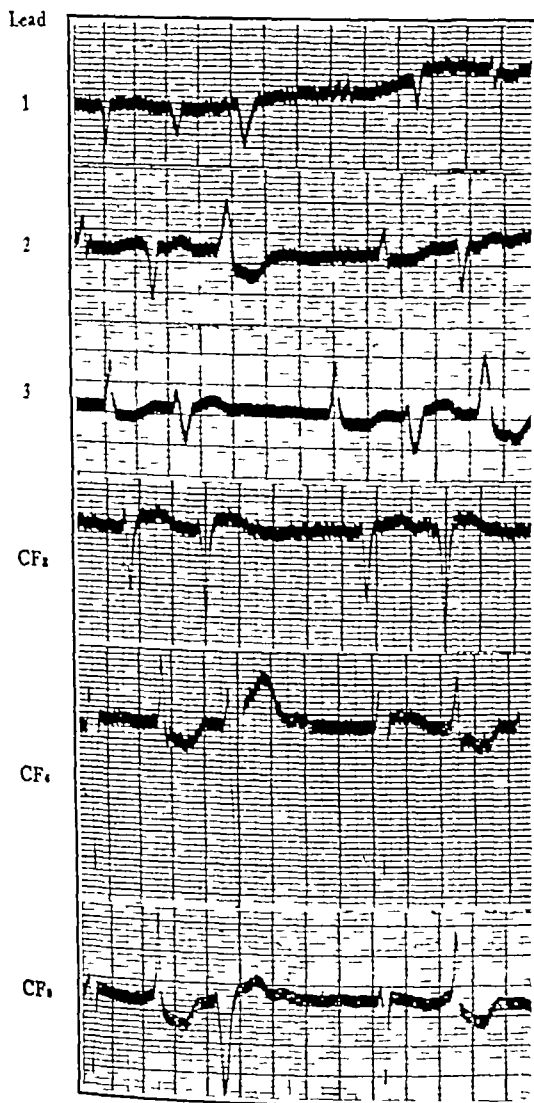


FIGURE 2

Was this a case of chronic bronchiectasis in a patient with asthma and shortness of breath on exertion, as well as at other times, due to pulmonary insufficiency and not to cardiac insufficiency? Or was the shortness of breath a cardiac symptom?

The swelling of the ankles indicates either myocardial failure or local stasis. We cannot tell at

this point whether the ankle swelling was equally bilateral. We must certainly think of the possibility of beginning heart failure. If due to beginning heart failure, did the swelling follow left ventricular failure, or was it primarily from right ventricular failure? The ankle swelling was thought to be of cardiac origin, for the patient took digitalis irregularly, for cyanosis as well as for the dyspnea.

He had auricular fibrillation, and of course with the history to this point one wonders about mitral stenosis. Since the left auricle was not large and since no murmurs were heard, we have some serious arguments against such a diagnosis.

He had increasing circulatory failure, probably myocardial in origin. I judge that from the age of seventeen until he was forty, when he began to have asthma, he had been quite well. Is that true? I believe that you know something about the history, Dr Sprague.

DR SPRAGUE: Yes, that is true.

DR WHITE: I assume that he was active and that he had never had high blood pressure.

DR SPRAGUE: That is so.

DR WHITE: "Physical examination revealed a florid, extremely cyanotic, obese, well developed man." That sentence has one important expression—that is, "extremely cyanotic." The degree of cyanosis was evidently impressive.

The wheeze is interesting. Was that due to pulmonary disease or pulmonary congestion from left ventricular failure? The description is not that usually seen with left ventricular failure and consequent pulmonary vascular engorgement.

The scleras were icteric. Did they become more definitely so, or did that remain a questionable sign?

DR SPRAGUE: They did not become more icteric.

DR WHITE: "The neck veins were full but not pulsating." That finding suggests considerable venous pressure and could go with the marked edema that the patient showed.

I assume that the large pulse deficit was due to the fact that the second and third beats of the bigeminy and trigeminy did not reach the wrist.

There were no murmurs. That statement should be underlined as being extremely important.

He showed evidence of hydrothorax, as well as a considerable amount of ascites. There is one sign not mentioned that I should like to ask about. Was there any clubbing of the fingers?

DR SPRAGUE: No.

DR WHITE: That is significant for certain reasons with reference to both the lungs and the heart. Certain kinds of congenital heart disease, particularly the tetralogy of Fallot, with considerable cyanosis and no pulmonary disease, are associated with clubbing, as is, of course, subacute bacterial endocarditis.

rate of about 120. The peripheral pulse was about 52. The heart sounds were loud, slapping at the apex and muffled in other areas. No murmurs could be heard when the patient was either reclining or sitting up. Examination of the chest revealed flatness and absent fremitus and breath sounds below the fourth interspace on the right posteriorly extending forward to the sternum at about the same interspace. A few moist inspiratory rales and soft expiratory rhonchi of the right lung were noted above this area. The left lung was clear except for a few moist rales at the base. The abdomen was much distended, moderately tense and revealed shifting dullness about half way up the flanks with a fluid wave. The liver could not be felt or balloted but was percussed three fingerbreadths below the costal margin. The spleen was not palpated but appeared slightly enlarged to percussion. The arm veins collapsed at a level about 10 cm above the sternum. There was severe pitting edema of both legs and the genitalia. A reducible left inguinal hernia extended into the scrotum. The blood pressure was 160 systolic, 80 diastolic.

Examination of the blood revealed a red-cell count of 5,520,000, with a hemoglobin of 17 gm, and a white-cell count of 8100, with a normal differential count. The urine had a specific gravity of 1.018 and gave a +++ test for albumin. The sediment contained a few hyaline and rare granular casts, a few red cells and 3 white cells per high-power field. The nonprotein nitrogen was 34 mg, and the total protein 7.1 gm per 100 cc. An x-ray film of the chest disclosed a large quantity of fluid in the right pleural cavity obscuring the right leaf of the diaphragm, the right border of the heart and the lower two thirds of the right lung field. There was a questionably small quantity of fluid in the left costophrenic angle, with an increase in the hilar shadows and prominence of the pulmonary vascular shadows. An electrocardiogram revealed auricular fibrillation at an average rate of 90 with frequent ventricular premature beats from different foci producing trigeminy in some places (Fig 2). There was a high degree of right-axis deviation. The T waves were low in Leads 1 and 2 and inverted in Lead 3, with a sagging ST segment in Lead 2. The T waves were low in Leads CF₁, CF₄ and CF₆, with deep S waves consistent with right-axis deviation.

A right thoracentesis yielded 1000 cc of clear yellow fluid, which greatly relieved the respiratory distress and on analysis contained 1.9 gm of protein, no white cells and 1129 red cells per cubic millimeter. The patient was given Purodigin and Digifolin. On the sixth hospital day about 30 cc of fluid tinged with bright-red blood was noted in the sputum, with increased cough. There was some boggy swelling, increased heat, redness and tenderness of the calf of the right leg that the patient admitted had been present for several weeks

but had recently subsided. No chest pain was noted. On the following day he appeared to have edema of the face and was drowsy, and a chest tap on the right again produced 1000 cc of clear amber fluid with a total protein of 3.8 gm, no white cells and 1100 red cells per cubic millimeter. On the eighth hospital day minimal right-calf tenderness was present, with only slight pitting edema. A surgical consultant believed that the calf tenderness and edema could be accounted for by heart failure and advised against vein interruption. Two days later, cyanosis was still noted. The patient refused any form of oxygen therapy. He did not prefer to sit upright in bed but lay almost always on the right side. Examination of the urine at that time revealed a + test for albumin with an occasional hyaline cast. The nonprotein nitrogen was 42 mg per 100 cc. By the fourteenth hospital day the cardiac rhythm had become normal. He continued, however, to have considerable chest fluid and ascites. Two days later, another 1000 cc of amber, slightly cloudy fluid was withdrawn from the right chest, 900 cc of similar fluid was taken from the abdomen. The chest fluid contained 1240 red cells and 90 white cells per cubic millimeter of which 70 per cent were polymorphonuclear cells. On the sixteenth day not much change had been noted. The heart sounds were surprisingly strong.

The patient had been refusing medication and continued to be markedly cyanotic. He had developed a decubital ulcer. On the following day another 1000 cc of fluid was removed from the right chest, and on the morning of the twentieth day he was again coughing up dark-red blood and appeared weak. The blood pressure was 100 systolic, 80 diastolic, and the pulse was about 80 radial and 100 apical. The lungs were essentially unchanged, and there was dullness on the right up to the level of the fifth or sixth rib posteriorly. On the following day he appeared still weaker. The blood pressure was 70 systolic, 50 diastolic. He became disoriented and finally unresponsive, with small convulsive jerks in the left arm and absent reflexes. Aminophyllin and continuous oxygen were without effect, and he finally died on the twenty-third hospital day.

DIFFERENTIAL DIAGNOSIS

DR PAUL D. WHITE. I am not at all sure whether any of the asthmatic attacks had anything to do with what followed. I wonder whether the patient had been studied particularly for this situation and whether we have any information about tests for allergy.

DR HOWARD B. SPRAGUE. He had not been tested.

DR WHITE. One wonders if the asthma was coincidental or part and parcel of the disease process.

DR WHITE The ectopic beats had disappeared, but the fibrillation may still have been present

DR SPRAGUE Yes, it was

DR WHITE The patient then showed a small pulse pressure, only 20 mm

This is certainly an unusual picture, and we must try to fit in several findings that are not often seen together. These are the years of asthma causing nocturnal orthopnea, the congestive heart failure, the deep cyanosis without finger clubbing, the auricular fibrillation (with many ectopic beats), the marked right-axis deviation apparent in the electrocardiogram, the absence of heart murmurs and the blood spitting. The last sign may have occurred terminally, there was no mention of early blood spitting.

One naturally thinks at once of the so-called "black cardiacs" or *cardiaques noirs* of Averza, or Averza's syndrome, which is more of a syndrome than a disease, in which the combination of pulmonary vascular disease and peripheral stasis secondary to right heart failure is responsible for the cyanosis. Bronchial asthma does not produce cyanosis, except in the rarest cases, of which I have not seen an example. I have always wondered if severe prolonged bronchial asthma might not come to us here, but the asthmatic patients that I have seen for years have not been cyanotic and have not died of heart failure.

Was this endarteritis obliterans (syphilitic, or more probably not)? We have not seen syphilitic endarteritis obliterans here. We have encountered endarteritis obliterans of the lungs, but so far as I know, it has been unexplained, so-called "idiopathic endarteritis." Periarteritis nodosa, or simply extensive fibrosis compressing or otherwise involving the arteries of the lung, must also be considered. Certainly, chronic cor pulmonale with final failure of the right heart is a strong probability. Can there have been not only terminal pulmonary infarction but also earlier repeated attacks in large part responsible for a chronic cor pulmonale? That is what we have seen here in rare cases — namely, attacks of repeated and extensive pulmonary embolism that can lead with survival to chronic cor pulmonale.

What else must one consider in the differential diagnosis? Could there have been mitral stenosis? That is possible, but I suppose that it is less likely than chronic cor pulmonale. To be sure, auricular fibrillation was present, but it should have set in years previously before failure developed rather than so late in life — the congestive failure came apparently before the auricular fibrillation.

DR BENJAMIN CASTLEMAN The patient was not examined at that time, and we do not know that the congestive failure was not present.

DR WHITE It was noted for a year but may have been present longer. Also, if there were enough mitral stenosis to produce such a clinical

picture as this, someone at some time should have heard a murmur. Although exceptions have been reported, I have never encountered a case of marked mitral stenosis without a murmur. Moreover, the left ventricular auricle was not large, and it looks as if there was too much right-axis deviation, although I have seen cases of this degree of right-axis deviation with mitral stenosis.

We must also consider congenital heart disease, but we do not know how long this patient had been cyanotic — probably not constantly since childhood, with this degree of cyanosis. The tetralogy of Fallot does not seem to be in keeping in this case, for this kind of history without clubbing of the fingers but with auricular fibrillation is not seen, so far as I know, in cases of tetralogy of Fallot. A large auricular septal defect is also a possibility — the patient was old for the tetralogy of Fallot, but not too old for an auricular septal defect, which may be almost symptomless until well into middle age. The strain of an overloaded pulmonary circulation can cause failure of the right side of the heart and death. Auricular fibrillation is a rare accompaniment of congenital heart disease but a possible complication in Lutembacher's disease, which consists of the combination of an auricular septal defect and mitral stenosis.

Then there are the rare conditions that should be thought of in any difficult case: tumors involving the heart, malignant or benign, for which we have no clue in this case, a mediastinal tumor compressing the pulmonary artery, and unusual infestation by parasites, which so far as I know does not produce such a picture as this except in dogs with filariasis involving the right heart and pulmonary arteries that causes a subacute cor pulmonale from plugging of the pulmonary arteries and right ventricle by the filarial parasites themselves. Malnutrition (beriberi), poisoning, endocrinopathy and myocarditis or other involvement of the right ventricle of unknown cause are some of the other rare conditions that should be thought of but not diagnosed in this case. Hypertension and atherosclerosis which primarily involve the left ventricle, do not fit, nor does thyroid disease or syphilitic aortitis, unless there was a bizarre, almost unique aneurysm of the ascending aorta compressing the pulmonary artery and causing a chronic cor pulmonale, of which we have seen a few cases. Constrictive pericarditis also seems to be out.

My diagnosis therefore rests between chronic cor pulmonale due to pulmonary endarteritis obliterans or to repeated pulmonary embolism or thrombosis with right ventricular failure and, second best, a congenital auricular septal defect, with or without mitral stenosis (Lutembacher's disease), which we are unable to diagnose because of the absence of a murmur, with failure of the right side of the heart, in either case complicated by digitalis toxicity and terminal pulmonary infarction. I am torn between

The blood studies did not indicate a polycythemia. That is important.

The urinary findings could have been due to renal congestion alone.

We must look into the degree of enlargement of the lung hilar shadows, the size of the left auricle and the condition of the mediastinum. May we see the x-ray films?

DR RICHARD SCHATZKI: We have only these two films taken at the time mentioned in the record. The large amount of fluid on the right side can be seen. It obscures completely the right border of the heart, which is unfortunate. From the film alone I am not sure that there was fluid in the left pleural cavity. The left lung is fairly large. Of what we can see of the pulmonary vessels the ones on the left side are almost completely obliterated but show some distention, which is also visible in the lateral view. The pulmonary conus is slightly prominent. The apex of the heart reaches farther to the left than normal. How much of that is due to enlargement of the heart and how much to displacement of the heart by the fluid is difficult to say from the film at hand.

DR WHITE: The heart was not so large as I thought from the earlier description on physical examination, but I suppose that there may have been some change at that time. There was still a moderate amount of space between the left border of the heart and the left chest wall. It was not one of the enormous hearts that one sees in mitral stenosis, in which the heart nearly fills the chest. Do you see any scars of pulmonary infarction?

DR SCHATZKI: Not in the small amount of lung that I can see.

DR WHITE: Is anything wrong with the aorta?

DR SCHATZKI: I can see just the edge of the arch of the aorta, and that is of approximately normal size for a patient of this age.

DR WHITE: The trachea is not particularly deviated?

DR SCHATZKI: It is normal in position.

DR WHITE: It is always unsatisfactory, for me at any rate, to read interpretations of electrocardiograms without seeing the actual film or print, just as it is with an x-ray film. Even without my asking, these electrocardiographic films were sent to me, so that I have a fair idea of the moderately high degree of right-axis deviation. It is not so marked as one sees with the tetralogy of Fallot. It is consistent with two or three other conditions. I think that generally we see a higher degree of right-axis deviation, including prominence of the S waves in the precordial leads with an auricular septal defect, although we have occasionally seen as much as this with a cor pulmonale. With mitral stenosis a moderate degree of right-axis deviation is occasionally found. The ventricular rate was rapid, — nearly 140, — so that that could have increased the degree of heart failure at the time, and it

looked as if there was considerable sagging of the ST segments, suggesting digitalis effect, although one would expect a lower rate if there had been a high degree of digitalis effect. That was the first film. There is a second tracing, described in the record, showing ectopic beats and producing a bigeminy and trigeminy. The usual ventricular complexes look much the same, and auricular fibrillation is present as in the first record, but we have an important change: the trigeminal ectopic beats alternate in appearance and move in opposite directions (Fig 2). This occurs regularly throughout the tracing, one might almost label it the beginning of paroxysmal ventricular tachycardia with beats alternating in direction. This is considered an unfavorable sign — an indication of toxicity close to that due to a fatal dose of digitalis. Was much digitalis being given at that time, Dr Sprague?

DR SPRAGUE: That is the rhythm with which the patient entered the hospital. The digitalis had been given outside and was omitted temporarily after admission, that did away with the toxic rhythm. The first electrocardiogram was taken a year previously.

DR WHITE: This unusual rhythm could have been the result of serious digitalis intoxication, but we have seen it in other extremely ill patients. Such irritability of the heart tends to lead to ventricular tachycardia and fibrillation and death.

What was the blood Hinton or Wassermann reaction?

DR SPRAGUE: It was negative.

DR WHITE: The electrocardiogram points strongly to marked enlargement of the right ventricle and is not the pattern of coronary heart disease, in which an inverted QRS wave in Lead I occasionally occurs. The QRS waves are narrow and are in keeping with right ventricular enlargement predominantly, rather than with coronary heart disease. One wonders if there was any suggestion of neoplastic disease in the thorax, for the fluid contained blood, but it was not the typical bloody fluid that one sees with neoplasm. I wonder how the Purodigin was given. Was it administered outside, and was there an interval before he received it again in the hospital?

DR FREDERIC C GOETZ: He refused medication for several days and was then given Digifolin intramuscularly.

DR WHITE: The patient then had what seemed like a thrombosis of the leg, with pulmonary infarction as a complicating factor.

"By the fourteenth hospital day the cardiac rhythm had become normal." Was that true according to the electrocardiogram, or thought to be true?

DR SPRAGUE: It was less irregular after the disappearance of the toxic rhythm.

DR WHITE In this case, if I had relied on the electrocardiogram alone, I would have made the correct diagnosis, since almost nothing other than considerable mitral stenosis of long standing can give rise to a pattern like this — namely, the combination of right-axis deviation and auricular fibrillation. The possibility of considerable mitral stenosis, however, with no murmur at all, little enlargement of the left auricle evident fluoroscopically and a high degree of cyanosis seemed even more exceptional, and I therefore chose to consider the electrocardiographic pattern as an exception to the rule. This case has stimulated us to investigate the relative rarities of these various exceptions

CASE 33132

PRESENTATION OF CASE

First admission A thirty-seven-year-old machinist entered the hospital because of a generalized rash, malaise and sore throat

Two months before admission and eight days after promiscuous kissing at a party a nontender lesion similar to a cold sore developed on the right lower lip. A succession of three lesions then appeared on the chin. A physician treated them with boric acid salve without improvement, another physician gave him penicillin salve after which the sores dried somewhat, but they never healed. A week before admission the patient developed a generalized rash with much malaise, sore throat and swelling of the lymph nodes in the neck.

Physical examination showed a generalized maculopapular eruption, mucous patches over the hard palate and cervical lymph-node enlargement. Colonies of *Treponema pallidum* were identified on dark-field examination of the lesion on the lip. The blood Wassermann reaction was positive. The patient was treated with 2,400,000 units of penicillin over a period of seven and a half days. The eruptions faded and he was discharged.

Final admission (eleven months later) Following discharge the patient was seen frequently in the Out Patient Department. No further treatment was carried out. The blood Hinton and Wassermann tests became negative in the course of several months, and he was symptom free until two months before admission. At that time he began to have attacks of headache, dizziness and a sense of burning and obstruction of the nose that were thought to be brought on by acid fumes inhaled from a soldering process at work, although they were admitted to have occurred on the street without apparent instigating cause. A month before admission there were several episodes of chills followed by nausea. The patient had visual hallucinations at work, seeing people in places where he knew they could not be. He had been drinking heavily, owing to worry about his illness. The visual hallucina-

tions ceased when he stopped drinking, but the other symptoms persisted. The headaches increased, centering especially just above the eyes. A week before admission he began to vomit occasionally, and the headache was so severe that sleep was impossible.

Physical examination disclosed a slightly disoriented patient complaining of photophobia and constantly rubbing his eyes. The abnormal physical findings were limited to the neurologic examination. There was moderate to marked tenderness over the right frontal sinus and antrum. The neck was not stiff. Odor perception was markedly impaired but not absent on the right, and was normal on the left, the air passages were not obstructed, nor was there any nasal discharge. Visual acuity on the right was 20/40, and on the left 20/50. The right pupil measured 3 mm, and the left 2 mm, both reacted slightly to light but not to accommodation. There was a completely congruous left homonymous hemianopsia with splitting of the macula lutea. The extraocular movements and the fundi were normal. The rest of the cranial nerves were normal. The left arm and leg were weak. The tendon reflexes were normal and equal on both sides. There was no ankle clonus. Pain, touch, position and vibration perceptions were normal.

The temperature was 99°F, the pulse 76, and the respirations 20. The blood pressure was 120 systolic, 80 diastolic.

The red-cell and white-cell counts and the hemoglobin were normal, and examination of the urine was negative. On lumbar puncture the initial spinal-fluid pressure was equivalent to 150 mm of water. The fluid was clear and contained 94 lymphocytes, 0 neutrophils and 0 red cells per cubic millimeter, the total protein was 125 gm, and the chloride 122 mg per 100 cc, the gold-sol curve was 0112223322. Two blood and spinal-fluid Hinton tests were negative. X-ray films of the skull and sinuses showed no erosion of the cribriform plate or other abnormalities. The electrocardiogram was "within normal limits" except for rather questionable disturbances on the right side, especially anteriorly toward the midline.

While in the hospital, the patient complained constantly of pain in the right frontal region and behind the right eye. Burning sensations in the right side of the nose occurred frequently. The hemiparesis and hemianopsia persisted. Lymphocytes were found on repeated lumbar puncture, and the spinal-fluid protein remained elevated. An operation was performed on the eighteenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR G COLKET CANER It seems to me that at the second entry the question that probably first preoccupied the house staff was whether the patient's symptoms were due to syphilis. He had had

these two interpretations I think that I favor the first, — namely, a chronic cor pulmonale, — but I would not be surprised to find the second, or indeed something else

DR SPRAGUE It is reassuring to have Dr White argue the same way as we did in this case I saw the patient only when he was extremely ill in the hospital Routine electrocardiograms were sent to the laboratory, and Dr Williams interpreted them as consistent with rheumatic heart disease He found that the house officer in requesting the electrocardiogram had made the diagnosis of rheumatic heart disease He then remembered that he had seen this patient a year before, when he was ambulatory and rapidly fibrillating prior to digitalization I asked him to examine the patient again We listened closely for a mitral diastolic murmur, but we were unable to hear it Knowing that the patient had been examined previously when not in extremis, we thought that we had further evidence that he did not have mitral stenosis In retrospect the one thing that we should have put more emphasis on and that I had put in my notes was that the first heart sound in this man remained louder, or at any rate of better quality, than he should have had when he was so sick

DR WHITE That makes me turn a little more toward mitral stenosis

DR SPRAGUE The heart sound was noted as loud by Dr Goetz, who said that the patient had mitral stenosis

DR DONALD S KING I thought from the history that this was not bronchial asthma The illness sounded circulatory to me

DR WHITE Do you usually find an exaggeration of symptoms in bronchial asthma at night?

DR KING Not as the history is given here It suggests mitral stenosis

DR CONGER WILLIAMS I should like to say that the cyanosis was the thing that led most of us to discard the diagnosis of mitral stenosis in favor of chronic pulmonary disease We did not believe that it was straight bronchial asthma but thought that it was possibly a lung condition, pulmonary fibrosis or something of that sort

DR SPRAGUE We thought that the patient might have had thrombosis of the pulmonary artery

DR ISAAC TAYLOR One striking thing on listening to the lungs was the severe prolongation of expiration, which persisted until the end and became marked

CLINICAL DIAGNOSES

Cor pulmonale
Pulmonary fibrosis and emphysema
Pulmonary infarcts

DR WHITE'S DIAGNOSES

Cor pulmonale, with congestive heart failure and auricular fibrillation or auricular septal de-

fect, with or without mitral stenosis (Lutembacher's disease)

Pulmonary infarction (terminal)

Digitalis intoxication

ANATOMICAL DIAGNOSES

Rheumatic heart disease, with severe mitral stenosis,

Cardiac hypertrophy, marked, right ventricle

Pulmonary infarct

Endocarditis, chronic rheumatic, slight, aortic and tricuspid

Cardiac and portal cirrhosis

Pulmonary emphysema, slight

Anasarca

PATHOLOGICAL DISCUSSION

DR CASTLEMAN We found 6000 or 7000 cc of fluid in the abdomen and a similar amount of fluid in the right chest There was none in the left pleural cavity In the apex of the right lower lobe there was an infarct that measured about 4 or 5 cm in diameter but no other infarct in the right lung and none in the left lung

DR WHITE Was there any suggestion of old scars in the lungs — that is, of infarcts?

DR CASTLEMAN No, the heart was large, weighing almost 700 gm The right ventricular wall was thick, measuring 1 cm, about three times the normal size The left ventricle measured 16 mm in thickness The tricuspid valve ring was markedly dilated, measuring almost 16 cm in diameter, and there was slight thickening and shortening of the chordae tendineae of one leaflet The dilatation of the right auricle was tremendous, measuring in one diameter about 14 cm We were unable to find any opening between the right and left auricles The mitral orifice was merely a rigid slit measuring 1 cm long and about 0.5 cm in its greatest diameter The valve was thickened and extensively calcified The left auricle was large and thick The aortic cusps showed some interadherence, but not enough to produce any appreciable stenosis There was therefore severe mitral stenosis and only minimal rheumatic involvement of the aortic and tricuspid valves

There was evidence of generalized chronic passive congestion The liver was somewhat large and was quite cirrhotic On microscopical examination, I believe that there was a combination of both cardiac and portal cirrhosis

DR WHITE The history of the auricular fibrillation is important in the absence of the murmur of mitral stenosis

DR CASTLEMAN There was a mural thrombus of the right auricle, which was probably the source of the pulmonary embolus, since the leg veins were free from thrombi Although the lungs showed some emphysema, I believe that mitral stenosis was responsible for the right-sided cardiac hypertrophy

not lay much stress on the lack of pupillary reaction to accommodation

A tumor at the base of the brain fairly often gives a number of lymphocytes in the spinal fluid, so that such a location would go with the spinal-fluid findings. A tumor in this region would not have to be large to cause the signs and symptoms presented, and a small tumor might account for the fact that the spinal-fluid pressure was not high.

Another possible location is the temporoparietal lobe, but a tumor there would have to be large to give a complete homonymous hemianopsia with splitting of the macula because the macular fibers in this portion of the optic radiations are well spread out. But a large tumor seems somewhat unlikely because of the localized headache and the low spinal-fluid pressure.

It therefore seems to me that the likeliest diagnosis is a tumor at the base of the brain involving the right optic tract and causing pressure on the spinal tract in the cerebral peduncle. I remember a case some years ago of a cholesteatoma in this region, but that is an unusual tumor, and I am not definite about the type of tumor in the case under discussion.

I am not sure enough of the location to suggest operation without a ventriculogram, and I imagine that that was done as part of the operation.

DR CHARLES S KUBIK Dr Rose, would you like to comment?

DR AUGUSTUS S ROSE I was on duty at the time the patient was admitted to the Neurological Service, and I might say that we went through the same type of reasoning as Dr Caner. As always, however, when the patient is seen one gets quite a different impression from that obtained on mere reading of the protocol. The first diagnosis that we considered was syphilitic meningitis. As was said at the time the proper diagnosis was made, a similar case would lead to a similar mistake. In other words, when a man who has had early syphilis adequately treated or presumably treated adequately and less than a year later develops headaches and lymphocytes in the spinal fluid, the case is syphilitic meningitis until proved otherwise. On the other hand this man was drowsy on admission. That was not emphasized in the record, and the history of alcoholism was somewhat more than is indicated. Subdural hematoma was our second diagnostic consideration, and yet the homonymous hemianopsia was against that. Finally, surgery became inevitable.

DR KUBIK As Dr Caner suggested, this patient had a ventriculogram before he was operated on. I suppose we might see the films now.

DR MILFORD SCHULZ These are rather representative films. One can see the entire ventricular system, somewhat increased in size and displaced to the left, the third ventricle as well as both lateral ventricles. The right lateral ventricle is pushed or displaced beneath the tentorium. The lateral view

is not helpful. The anteroposterior view seems to be the most useful and indicates a large space-occupying lesion in the right hemisphere, probably in the temporoparietal region.

CLINICAL DIAGNOSIS

Syphilitic meningitis?

Subdural hematoma?

DR CANER'S DIAGNOSIS

Brain tumor, type undetermined

ANATOMICAL DIAGNOSIS

Glioblastoma multiforme, right temporal lobe

PATHOLOGICAL DISCUSSION

DR KUBIK A right temporal-lobe tumor was found at operation. Biopsy diagnosis at operation indicated that it was glioblastoma multiforme, and no attempt was made to remove it. The patient remained in coma and died on the third or fourth postoperative day.

DR LEWIS K DAHL May I ask if the symptoms that Dr Caner interpreted as evidence of fifth-nerve involvement might not have represented attacks of uncinat epilepsy?

DR ROSE I might say in that connection that before operation the sensations that the patient called pain were thought to be attacks of uncinat epilepsy.

DR KUBIK Lantern slides of serial coronal sections of the brain showed a tumor in the lower medial portion of the right temporal lobe. The cut surface had the necrotic grayish-yellow appearance that is characteristic of a glioblastoma multiforme. The tumor was in close relation to the third nerve, and it is rather surprising that there was not more evidence of third-nerve involvement than a slightly enlarged pupil. Its close proximity to the cortical spinal tract in the cerebral peduncle probably accounted for the hemiparesis, and the involvement of the optic tract lateral to the peduncle explained the homonymous hemianopsia. An interesting feature was the invasion of all the subependymal tissues outside the lateral ventricles by tumor. Histologically, the tumor was a glioblastoma multiforme. In many places there was infiltration of the subarachnoid space with a few plasma cells. There was some perivascular lymphocytic infiltration in the medulla. The cellular infiltration at a distance from the tumor, taken in connection with the history, was suggestive of syphilis.

DR JAMES A MEATH In answer to Dr Dahl's question, I would like to say that it was because this patient had attacks of uncinat epilepsy that he was treated on the Neurological Service. The symptom of difficulty in smelling was also possibly due to the tumor.

DR KUBIK The tumor invaded the uncinat gyrus and so created a condition in which attacks of uncinat epilepsy might have occurred.

primary and secondary syphilis about a year previously, and the treatment given at that time is generally considered to be the minimal adequate penicillin treatment in early secondary syphilis. Dr. Rose tells me that such treatment can be expected to give a cure in a high percentage of cases but that at present a course of bismuth injections would undoubtedly be given at the same time. The fact that the blood Hinton test changed to negative indicates that the treatment was probably adequate in this case. But we have no spinal-fluid examination, and in a case with secondary syphilis a spinal-fluid examination ought to be made six months after treatment and again a year later because during the secondary stage of syphilis the central nervous system is invaded and one cannot be sure that treatment adequate to change the blood Wassermann and Hinton reactions to negative will also be adequate to eradicate the infection from the nervous system. In this case there was no spinal-fluid examination prior to the second entry so that the staff could not have been entirely sure that the treatment given had been adequate.

Irrespective of whether the patient's syphilis was treated adequately there is evidence that the patient himself was not treated adequately because he apparently worried so much about his illness that he began drinking heavily. It is, of course, important not only to treat the illness but also to treat the patient. In particular the patient should be helped to take his illness well and to react well also to other things in his life that might be upsetting to him. The physician can often contribute more in this direction than he can in treating a disease itself.

Going back to whether or not the patient's symptoms were due to syphilis, although the spinal-fluid examination showed a number of changes characteristic of syphilis, — namely the high lymphocyte count, the high total protein and the change in the gold-sol curve, — there were two negative spinal-fluid Hinton tests. Sometimes in syphilitic meningitis the Hinton test is negative at the first spinal puncture but at the second puncture the test is almost always positive. In a syphilitic meningitis, the blood Hinton reaction is also almost always positive, and the fact that there were two negative blood Hinton tests is also strong evidence against syphilis. Additional evidence against syphilis is the fact that the total protein was higher than one would expect with this lymphocyte count, if the count were due to syphilis. A count of 94 lymphocytes per cubic millimeter due to syphilis would be accompanied by a total protein of 55 or 60 rather than one of 125 gm per 100 cc. It is also hard to explain the homonymous hemianopsia on the basis of meningovascular syphilis or of syphilitic meningitis. A syphilitic meningitis would also cause a stiff neck and a generalized headache, whereas this man's headache was fairly well limited to the orbital

region and to the supraorbital and infraorbital regions. For all these reasons I think that syphilis can be ruled out.

If syphilis is not the diagnosis, what else could have caused the spinal-fluid findings? As possibilities one might think of poliomyelitis and multiple sclerosis, but obviously the history does not suggest either diagnosis. One thinks also of brain abscess, but in brain abscess one would expect a number of neutrophils in the spinal fluid in addition to the lymphocytes. Also, the total protein was rather high in comparison to the number of cells for brain abscess. I therefore think that brain abscess is unlikely, too.

Then one comes to tumor, and it seems to me that tumor is the likeliest diagnosis. Tumor, of course, frequently gives a high protein and with the high protein there can be changes in the gold-sol curve. Tumor does not often cause such a high lymphocyte count in the spinal fluid, but it may do so and when it does polymorphonuclear leukocytes are usually present in addition to the lymphocytes. But sometimes the increased count in the spinal fluid is limited to lymphocytes, as in this case.

If the spinal-fluid changes were due to tumor, where was the tumor located? It seems to me that the most definite finding that we have to go on is the homonymous hemianopsia with splitting of the macula, which is usually caused by a lesion located where the macular fibers are well bunched, they are well bunched either at the extreme posterior part of the occipital lobe or in the optic tract. If the lesion had been in the extreme posterior part of the occipital lobe it seems to me that it would be hard to explain the left hemiparesis, and the dilated right pupil would also be hard to explain in the absence of marked pressure. It would perhaps be possible to account for the fact that the headache was centered in the back of the orbit because the tentorium is innervated by the fifth nerve and sometimes pressure on the tentorium causes referred pain to the back of the orbit. If, however, the tumor were located at the base of the brain involving the right optic tract and causing pressure on the right cerebral peduncle it could readily explain the picture. A lesion there could involve the third nerve, causing a slightly dilated pupil, it could also involve the trigeminal nerve and give rise to extreme pain in the orbit and in the supraorbital and infraorbital regions and perhaps to the stinging pain in the nose. A lesion in this region would not account for the failure of the pupils to react to accommodation, but this finding is hard to explain by any lesion that would also cause a homonymous hemianopsia. Patients often do not try to focus the eyes on a finger held close to their eyes, however, and if they do not there is no reaction to accommodation. To get patients to focus one may have to ask them, for instance, to tell the time by looking at a watch held close to the eyes. I therefore do

THE "VOLUNTARY HOSPITAL"

ONE of the more important talks presented at the Massachusetts General Hospital's Ether Day Centenary last October was that of Dr. Nathaniel W. Faxon, director of the hospital, entitled "The Voluntary Hospital — How Can It Survive in the Modern World?" This paper, which is published elsewhere in this issue of the *Journal*, merits particular attention because it concerns us all, doctor and layman alike.

The term "voluntary hospital" is applied to non-profit, nonpolitical institutions, praiseworthy common in this country, that have been established as philanthropic organizations, designed for the common good. As leaders in their field from the start, they have set the pace and made the advances. That the Massachusetts General Hospital should be a leader and a pioneer among the hospitals of this type is purely circumstantial, it does not affect the point of Dr. Faxon's argument.

The point is that the question of the survival of the voluntary hospital is now before us to be answered, and that question applies particularly to the most valuable and consequently the most costly of these institutions — the hospital that adds to its service of caring for the sick the services also of scientific research and of training medical, nursing and technical personnel.

The high cost of dispensing these services has always been met, precariously, by two sources of income. The lesser of these has been the payment for services from patients and from agencies responsible for patients. The greater and more important has been derived from the gifts received perennially from well-to-do and philanthropically minded persons. As a result of increased taxation and decreased available incomes, the latter vital revenue is drying up at the source. The will may still be present, but, to make practical a familiar quotation, the giver without the gift is bare.

An actual injustice generally prevails, moreover whenever third parties enter into the contract between hospital and patient — state, city and town departments of welfare, a variety of federal agencies and the insurance companies operating under workmen's compensation acts. None of these, so far as we can say at the moment, despite their avowed

commitments, have ever met their financial responsibilities in full. The deficits that they leave have to be met by hospital funds, sometimes from principal and sometimes from the revenue derived from community-chest allotments. It should be as much a source of shame as it is of sorrow that the insurance companies and the governmental agencies are willing to rely for the fulfillment of their contracts on the meager funds of charitable hospitals.

Since hospitals can no longer continue to make up the difference between the costs of caring for patients and the part of the costs that governmental and other agencies have so far been willing to discharge, and since the better hospitals are loath to settle for less expensive and lower grade care for such beneficiaries, it seems high time that these agencies prepared themselves to pay in this respect full price for what they are receiving.

MASSACHUSETTS MEDICAL SOCIETY

TREASURER'S REPORT COVERING REFUND DISTRIBUTION

The Treasurer of the Massachusetts Medical Society makes the following report regarding the refund to district societies for 1947:

The Council voted to distribute the sum of \$4000 to district societies. The total number of payments of annual dues received by the Treasurer by March 1, to be counted for the refund, was 4527. Therefore, the refund to the district societies for each paid fellow is \$0.8836.

The following table gives the number of payments, as of March 1, and the refund to each district as of March 17:

DISTRICT	NUMBER	REPORTED	PAID	REFUND
Barnstable	44			38.88
Berkshire	127			112.21
Bristol North	66			58.31
Bristol South	181			159.93
Essex North	175			154.63
Essex South	261			230.62
Franklin	40			35.34
Hampden	301			265.96
Hampshire	64			56.55
Middlesex East	135			119.28
Middlesex North	114			100.73
Middlesex South	918			811.14
Norfolk	818			722.78
Norfolk South	138			121.93
Plymouth	130			114.87
Suffolk	566			500.11
Worcester	367			324.28
Worcester North	82			72.45
	4527			\$4000.00

In 1946, for comparison, the total number of payments for the refund was 3965.

ELIOT HUBBARD, Jr., M.D., Treasurer

DEATH

ELLISON — Daniel J. Ellison, M.D., of Lowell, died suddenly on February 14. He was in his sixty-second year. Dr. Ellison received his degree from Tufts College Medical School in 1908 and practiced in Alton, New Hampshire, before

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

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PUBLISHED UNDER THE JURISDICTION OF THE
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United States (medical students \$3.50 per year), Canada \$7.00 per year
(Boston funds), \$8.50 per year for all foreign countries belonging to the
Postal Union.

MATERIAL should be received not later than noon on Thursday, two
weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any
contributor.

COMMUNICATIONS should be addressed to the *New England Journal of
Medicine*, 8 Fenway, Boston 15, Massachusetts.

CANCER MONTH

THE designation of April as Cancer Month is assuming greater significance each year. As *Cancer Facts*, a pamphlet published a year ago by the Metropolitan Life Insurance Company, points out, the cancer death rate per 100,000 population increased from 64.0 in 1900 to 120.3 in 1940. This does not necessarily mean that cancer in any particular age group is becoming more prevalent, but it does indicate that the percentage of persons in the older age groups has markedly increased and that there has been an improvement in diagnostic procedures. In 1943, cancer was the most frequent cause of death in women thirty-five to fifty-four years old, and the second most frequent in those fifty-five to seventy-four, it was second in men from forty-five to seventy-four. Death rates are highest in the large cities, and lowest in rural areas, which merely points out that

more cases are diagnosed in places where adequate medical facilities are widely available. In women, approximately 40 per cent of cancers occur in the digestive tract, and a like percentage in the genital organs, including the breasts. In men, more than 50 per cent of cancers are found in the digestive tract, with about 20 per cent in the genitourinary tract and over 10 per cent in the lungs. Among the industrial policyholders of the Metropolitan Life Insurance Company, there has been a steadily increasing downward trend in cancer deaths among women, and there has even been a slight drop among men in recent years.

All these facts serve to emphasize the need for the early diagnosis of cancer, and its prompt treatment. It is well known that at least 80 per cent of women with breast cancer can be cured if a radical operation is performed before the malignant growth has spread to the axilla through the lymphatic vessels. That a "lump" in the breast is easily recognizable by the patient and that women have become increasingly aware of the significance of such a lump are undoubtedly largely responsible for the decrease in deaths from cancer among women, but many cures of cancer in other locations could be effected if the persons could be educated to undergo semiannual or annual physical examinations and also to go to a physician when certain symptoms are experienced.

In the past, cancer education by state departments of health and by organizations such as the American Cancer Society has been chiefly directed to the public. It is becoming more and more apparent, however, that the general practitioner and other physicians who see relatively few cases of cancer each year should be kept well informed concerning the most recent advances in diagnosis. For this reason the American Cancer Society has decided to issue a monthly publication *Cancer*, which will be sent to all practicing physicians in the United States. In this way it is hoped that physicians will become increasingly aware of symptoms that suggest cancer, that their patients will be warned concerning the need for reporting such symptoms, that all such cases will be referred, if necessary, to someone properly qualified to make the diagnosis and to give treatment and that the number of deaths due to cancer will markedly decrease.

The New England Journal of Medicine

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Volume 236

APRIL 3, 1947

Number 14

THE PROBLEM OF SOCIAL MEDICINE: EQUILIBRATING THE DISTRIBUTION AND TECHNOLOGY OF MEDICAL CARE*

WINSLOW CARLTON

NEW YORK CITY

NO SUBJECT calls more insistently than social medicine for a disclaimer of omniscience. Medicine as a social institution is peculiarly complex both in structure and in function. This paper essaysonly to indicate the nature of a central problem and to suggest a few principles for guidance toward solution.

Throughout the United States today, one element in the distribution of medical care is under sharp attack. Strong political forces are pressing for a new way of paying for medical services. On the principle that all people have an equal right to the benefits of medicine, it is proposed that the Government cover the costs. Although many opponents believe that the movement "to socialize" medicine, as the attempt has been labeled, reflects no more than the desires of a small but vocal radical group, there is substantial evidence that the prevailing system for distributing medical care is not, in fact, appropriate to the technology of medicine.

To put it bluntly, the present system does not succeed in delivering to most people anything like the scope and quality of services of which modern medicine is capable. Formal sociologic studies conducted over the past thirty years provide statistical evidence in support of that conclusion, and observation of medical conditions in a variety of communities confirms it. There is no need to enumerate the quantitative findings; the principal ones have been conveniently assembled in a publication of the Social Security Board entitled "Medical Care and Costs in Relation to Family Income." What should be said is that these statistics require interpretation in the light of clinical observations. Without a knowledge of how medicine, as a social organism, actually functions, it is easy to conclude that a great deal of money collected and disbursed by the community at large will effect a cure.

Observation of conditions in New York City leads, I believe, to substantial modification of that con-

clusion. There it is true, are most of the medical prerequisites although it could do with more of almost everything, New York is rich in medical resources compared with many other communities. It must be added that the impressions recorded below have been distilled from the experience of eight years' effort to establish a voluntary system of prepayment for medical care in New York City.

The undertaking offers considerable advantages for purposes of observation, since such prepayment plans deal with both the suppliers and the recipients of medical and allied services. Enterprisers in this field—they might be called "adventurers" if one had a mind to, and many doctors have—are necessarily observers of how medicine actually works. One sees physicians in practice and learns what they expect of medicine and what they realize, concurrently, the patients disclose what they expect of medicine, how they go about getting it and what they get.

* * *

Our first conclusion is that nearly half the cases of illness occurring among New Yorkers of average income do not reach a physician or any other person of medical experience. With our wealth of resources,—including physicians, hospitals, clinics and social services,—virtually all emergency cases receive medical attention. No such statement, however, can be made about other illnesses. The evidence for this conclusion comes from experience with a prepayment plan operated by Group Health Insurance from 1938 to 1944 that was almost identical in scope of services with that of Boston's recent White Cross plan. It covered virtually all types of physician's care. Any licensed physician was eligible to participate, and a panel of three hundred and fifty general practitioners and a hundred and fifty specialists was developed. The maximum number of subscribers enrolled at any one time never exceeded fifteen hundred. The plan, obviously enough, was not a practical success, but something was learned about the existence of un-

*Presented at a symposium "The Hospital in the Community" held during the Ether Day Centenary of the Massachusetts General Hospital, Boston, October 16, 1946.

†Chairman, Health Insurance Incorporated, New York

moving to Lowell. Of late years he had limited his practice to internal medicine, being particularly interested in diseases of the heart. He had always been active in the affairs of the Middlesex North District and Massachusetts medical societies having been a counselor for many years, as well as a member, and often the chairman, of several important committees. He was a senior physician at the Lowell General, St. John's and St. Joseph's hospitals, a member of the American Heart Association and the New England Obstetrical and Gynecological Society and a fellow of the American Medical Association. His widow and a daughter survive.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

FOX — George L. Fox, M.D., of Exeter, died recently. He was in his fifty-ninth year.

Dr. Fox received his degree from McGill University Faculty of Medicine in 1924. He was a fellow of the American Medical Association.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

CLINIC	DATE	CLINIC CONSULTANT
Haverhill	April 2	William T. Green
Lowell	April 4	Albert H. Brewster
Salem	April 7	Paul W. Hugenberger
Gardner (Worcester subclinic)	April 8	John W. O'Meara
Brockton	April 10	George W. VanGorder
Greenfield	April 14	Charles L. Sturdevant
Springfield	April 15	Garry deN. Hough, Jr.
Pittsfield	April 16	Frank A. Slowick
Worcester	April 18	John W. O'Meara
Hyannis	April 24	Paul L. Norton
Fall River	April 28	David S. Grice

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Chemistry of Anesthesia By John Adriani, M.D., director, Department of Anesthesia, Charity Hospital of Louisiana at New Orleans, and clinical professor of surgery, Louisiana State University of Medicine. 8°, cloth, 535 pp., with 45 illustrations. Springfield, Illinois: Charles C. Thomas, 1946. \$7.00.

Diagnostic Examination of the Eye. Step-by-step procedure By Conrad Berens, M.D., professor of clinical ophthalmology, Columbia University, executive eye surgeon, New York Eye and Ear Infirmary, and managing director, The Ophthalmological Foundation, and Joshua Zuckerman, M.D., C.M., instructor in ophthalmology, New York Eye and Ear Infirmary and Columbia Postgraduate School, ophthalmic surgeon, Midtown Hospital, and assistant ophthalmic surgeon, New York Eye and Ear Infirmary. 8°, cloth, 711 pp., with 410 illustrations. Philadelphia: J. B. Lippincott Company, 1946. \$15.00.

It's How You Take It By G. Colket Caner, M.D., associate in neurology, Massachusetts General Hospital, and psychiatrist in the Department of Hygiene, Harvard University. 12°, cloth, 152 pp. New York: Coward-McCann, Incorporated, 1946. \$2.00.

Diseases of the Retina By Herman Elwyn, M.D., senior assistant surgeon, New York Eye and Ear Infirmary. 8°, cloth, 587 pp., with 170 illustrations. Philadelphia: Blakiston Company, 1946. \$10.00.

Roentgen Diagnosis of Diseases of the Gastrointestinal Tract By John T. Farrell, Jr., M.D., clinical professor of radiology, Graduate School of Medicine, University of Pennsylvania, radiologist, Hermann Hessenbruch Memorial Department of Radiology, Lankenau Hospital, radiologist, Children's Hospital of the Mary J. Drexel Home, roentgenologist, White Haven Sanatorium, consulting roentgenologist, Frederick Douglass Memorial Hospital, and consulting roentgenologist, Mercy Hospital. 8°, cloth, 271 pp., with 190 illustrations. Springfield, Illinois: Charles C. Thomas, 1946. \$5.50.

Sex Problems of the Returned Veteran By Howard Kitching, M.D. With a foreword by Ernest R. Groves, professor of sociology, University of North Carolina. 12°, cloth, 124 pp. New York: Emerson Books, Incorporated, 1946. \$1.50.

Music in Medicine By Sidney Licht, M.D. 8°, cloth, 132 pp. Boston: New England Conservatory of Music, 1946. \$3.00.

Agnosia, Apraxia, Aphasia. Their value in cerebral localization By J. M. Nielsen, M.D., associate clinical professor of medicine (neurology), University of Southern California, and senior attending physician in neurology and assistant in neuropathology, Los Angeles County Hospital. Second edition, completely revised. 8°, cloth, 292 pp., with 59 illustrations. New York: Paul B. Hoeber, Incorporated, 1946. \$5.00.

Human Embryology By Bradley M. Patten, M.A., Ph.D., professor of anatomy, University of Michigan. School. 8°, cloth, 776 pp., with 446 illustrations. Philadelphia: Blakiston Company, 1946. \$7.00.

Hippocratic Wisdom. For him who wishes to pursue properly the science of medicine. A modern appreciation of ancient scientific achievement By William F. Petersen, M.D., Chicago. 8°, cloth, 263 pp. Springfield, Illinois: Charles C. Thomas, 1946. \$5.00.

Clinical Roentgenology of the Heart By John B. Schwedel, M.D., associate attending physician, Medical Division, and adjunct attending physician, Department of Roentgenology, Montefiore Hospital, New York City, and attending electrocardiographer and associate visiting physician in medicine, Gouverneur Hospital, New York City. *Annals of Roentgenology*, Vol. XVIII. 749 illustrations. New York: Paul B. Hoeber, Incorporated, 1946. \$12.00.

Diseases of the Adrenals By Louis J. Soffer, M.D., adjunct attending physician, Mount Sinai Hospital, New York City. 8°, cloth, 304 pp., with 42 illustrations and 2 colored plates. Philadelphia: Lea and Febiger, 1946. \$5.50.

Ophthalmology in the War Years Edited by Meyer Wiener, M.D., professor of clinical ophthalmology, Washington University School of Medicine. Volume I (1940-1943). 8°, cloth, 1166 pp. Chicago: Year Book Publishers, Incorporated, 1946. \$13.50.

NOTICES

SUFFOLK CENSORS' MEETING

The Censors of the Suffolk District Medical Society will meet for the examination of candidates at the Boston Medical Library, 8 Fenway, on Thursday, May 1, at 4:00 p.m.

NEW ENGLAND OBSTETRICAL AND GYNECOLOGICAL SOCIETY

The spring meeting of the New England Obstetrical and Gynecological Society will be held in Providence on Wednesday, April 30. Clinics will be held at the Rhode Island Hospital and the Providence Lying-in Hospital. Dinner will be served at the Squantum Club.

(Notices continued on page xxiii)

from which his profession sprang. He cannot be merely the technician, processing each patient who appears before him on the production line.

A further point of criticism is that a considerable amount of medical care rendered under present conditions is mechanical. Patients reporting to the outpatient departments of some teaching hospitals are not uniformly treated with consideration and respect, although given all possible laboratory tests and x-ray examinations. In the New York plan, we found more physicians possessed of technical competence than those also equipped to deal with their patients as people. It seems likely that this has a bearing on the failure of the public to seek preventive services and to maintain consistent medical relations.

Anything done in the future should certainly be designed to avoid sterile mechanization. Rather, the conditions under which medical service is rendered should provide incentive for the development of the personal relation between physician and patient. If this could be accomplished, there is no doubt that more emphasis would be placed on the education — in contradistinction to the training — of those entering medicine and that psychology and psychiatry would receive more attention both in the curriculum and in research than they are now accorded.

The second requirement placed on reform must be in the interest of the physical sciences. This is given second place because scientific development is in large part a function of broader forces than medicine controls. It ebbs and flows with basic social and economic conditions, and so long as America remains economically strong and socially dynamic, great energy and large resources will be channeled into basic scientific research. But the system of medical distribution should contribute to the multitude of undertakings required either to adapt the products of pure research to medical use or to investigate the nature and causes of disease. At present, only from the distribution of drugs and medicines is there a financial contribution to research that stems directly from the users. Otherwise, the distributive system does not automatically produce the sinews of development. For the rest, medical research is dependent on the charity of individual physicians donating time, of philanthropists providing endowments and of foundations making grants. A small amount, which may soon be larger if current efforts in Washington succeed, comes from government. Clearly, it is not inherent in the nature of medicine to depend on benefactions for so vital a part of its work. It is merely that society has not yet caught up with the change that has taken place since the principal source of medical care was the church. No one suggests that voluntary contributions to the cause of medicine should not be welcomed, it is only that the degree

of dependence on charity is no longer appropriate to the task.

It should be added that since the public is now orientated toward medicine, an additional charge labeled "for scientific research" on bills for professional or hospital services would probably meet with less resistance than an equal charge for personal preventive services.

The financing of hospitals has more nearly kept pace with their evolution than has that of research. Here, a change of functions since the days when hospitals were pesthouses and hostels is obvious. As prime requisites in both the production and the distribution of medical care, the distributive system should effect adequate means of support. To make up present deficiencies in certain parts of the country, the expedient of federal aid as embodied in the Hill-Burton Act, recently adopted by Congress, seems desirable, but it would surely be functionally and organically sounder to place hospital financing directly into the total medical scheme. We are well on the way to doing that, the deficits of our voluntary hospitals in New York are down to less than 10 per cent of operating costs.

Obviously, a reformed system of distribution should contribute more than money to the development of medical research. It should be so constructed that physicians and others with a bent for investigation are given an opportunity to participate in systematic research without having to establish themselves in a metropolitan center. Smaller communities need that caliber of professional ability and interest. The mechanical difficulties involved are obvious and great, but the concept of central hospitals with satellite institutions and staffs is already current and attempts to apply it have been started.

* * *

The final criteria of an adequate distributive system for medicine are both economic. In the first place, the personnel and facilities should be organized for maximal efficiency, and secondly, the cost of producing and distributing medical care should be equitably apportioned.

The word "efficiency" carries a connotation of regimentation and mechanization that it ill deserves. That is efficient which most directly accomplishes the purpose. The purpose under consideration is to provide a complex personal service, whose main elements I have attempted to define. Thus, it would not be efficient medicine for this hospital to employ ten doctors from nine to five for five days a week to give physical examinations and only physical examinations. By the same token, it is not efficient medicine — no matter how great the apparent saving in dollars — to rotate clinic staffs in such a way that each time a patient visits the clinic he is seen by a different physician.

treated conditions and what happens when the barrier of fees is removed

One feature of the plan was a preadmission medical examination conducted by general practitioners selected from the panel by the applicant, and it should be noted that the Medical Board found a great variation in the quality of the examinations. According to the reports submitted, conditions requiring medical attention were found in 30 per cent of the applicants, and the nature of the conditions suggested that fully a third of these had not received such attention. When it is considered that the majority of the subscribers were acutely conscious of their health or at least more aware of medical care than the average person, as indicated by the fact that they had joined the plan, it is evident that a substantially higher proportion of the population at large are avoiding medical attention.

After admission to the plan, the subscribers averaged about six yearly calls on a general practitioner—that is, the participating physicians had six hundred calls per hundred subscribers, of which five hundred and fifty were in the office and fifty at home. It has been reliably estimated that this over-all figure represents about double the number of services used under postpayment. The participating physicians who had the largest practices reported only a negligible amount of hypochondria or abuse of privilege among the subscribers, the overwhelming majority of calls were for illness, organic or functional, that needed medical attention. Although many of the conditions were not important, others were, and the uninformed patient had no way of distinguishing one from the other except through pain.

The second, and more surprising, fact disclosed is that interest in and concern for the maintenance of the patient's health is the exception, not the rule, among general practitioners. The reason is not far to seek: there is little effective demand for personal preventive medicine. Whatever the practitioner may have learned at medical school and the hospital, the services for which patients seek care and pay determine the direction of his interest. The treatment of acute upper respiratory infections, gastrointestinal disorders and children's diseases, the reduction of fractures and dislocations and attendance on obstetric cases comprise the average general physician's practice. Thorough physical examinations and, except for hypochondriac patients, consultation on general conditions of health are not sought.

Also impressive was the contrast between the co-ordination of care effected by practitioners affiliated with leading hospitals when their patients needed specialist attention and the lack of co-ordination in similar cases when handled by practitioners without good hospital connections. Numerically, almost a quarter of the subscribers were judged by the general physicians to require some type of specialist

service in the course of a year. It is believed that closer association between practitioners and specialists, such as that created by group practice, would raise this proportion, high though it already seems in comparison with the 15 per cent often cited.

Finally, the most striking phenomenon observed is the degree of ignorance shown by people in all walks of life concerning both what medicine has to offer and how to go about obtaining medical attention. Only about a third of the people in New York have a family physician, according to a survey made several years ago. Whereas this proportion is doubtless lower than would be found elsewhere, there is little doubt that the institution of the family doctor has declined sharply the country over during the past quarter century, and nothing has taken its place. The result is that an ever-increasing number of people are medically adrift. In the classic sense of the term, they might be called the "medical proletariat." To these people, physicians are to be called, like the fire department, in emergencies only. And when the emergency arises, they find that they do not know whom to call. There is evidence of a growing reliance on hospitals as sources of medical referral, but the testimony of a relative or friend, the corner druggist or merely the shingle by the door is usually decisive.

Still another sign of dislocation is the drift of these unattached patients to specialists, or to those whom they believe to be specialists. Everyone who is not a physician has great faith in his ability to diagnose his own ailments, and the patient with a backache is taken to "Mrs. Smith's wonderful bone specialist." An internist of my acquaintance wryly remarked that in a surprising number of these self-referred cases, the patient's diagnosis is confirmed.

* * *

This review of deficiencies in the distribution of medical care, fragmentary and impressionistic though it is, may seem an effort to frame an indictment. It is not; the purpose is rather to delineate a problem. American medicine as a social institution is out of balance: the medical arts and sciences are capable of far more than the distributive system delivers. And in one broad and important field—namely, the conservation of personal health—the limitations of distribution are reducing technology to a state of virtual atrophy.

The question now facing us is how, precisely, to reform the system of distribution to provide better, as well as more, medical care. Certainly, the answer is not a simple one. Anyone who has been closely associated with medical care must realize that much that is actually and potentially best in medicine is volatile. For all that the physical sciences have contributed to diagnosis and treatment, a large part of the physician's technic is the product of art rather than of laboratory science. The physician retains many of the attributes of the priesthood.

staffs of men and women working in the community, observing medical conditions with painstaking care, consulting the experience of representative people, examining the results of local medical plans and interpreting their findings as scientists will produce sound answers to the fundamental questions at issue.

The problem of social medicine is now acute, but so long as American society remains dynamic, the

problem will also be chronic. Changes in general society and within medicine itself will call for constant adjustment of the distribution and technology of medical care to maintain a balance. Only consistent, scientific examination of the people's health and evaluation of the findings in the light of broad social understanding will achieve the flowering of medicine that now lies in the wood.

THE TEACHING HOSPITAL'S SERVICE TO THE PUBLIC*

ALLAN M. BUTLER, M.D.†

BOSTON

THAT ether was introduced into the practice of medicine in a hospital such as the Massachusetts General Hospital was not an odd chance. Such a large teaching general hospital provides the various factors essential to the intelligent introduction of new therapeutic agents and technics to medical practice. Indeed, the actual application of all new medical knowledge must almost always be accomplished through such a hospital. Where else can be found an adequate number of patients under the close and continuous observation of competent physicians who have the appropriate training, the curiosity, the time and the support of adequate laboratory facilities and personnel? The fact that such therapeutic agents as x-rays, radium, the sulfonamides, penicillin, streptomycin and the radioactive isotopes were introduced into medicine through teaching hospitals demonstrates their particular suitability for determining the methods by which the contributions of science may be applied to the care of patients. Moreover, the clinical investigator is often the first to see the clinical application of scientific knowledge. Although his role usually falls under the category of applied science, his contact with both clinical medicine and scientific thought and technic gives him interests and opportunities that the basic scientist may not have. The experimental contributions of the clinical investigator, therefore, may open fields that basic science and industry may cultivate with great profit.

The discovery of the anesthetic value of ether by Long, a physician, and Morton, a dentist, that is commemorated today opened a field of scientific investigation to chemists and physiologists that was effectively cultivated by industry to the great benefit of society. Banting, an orthopedic surgeon, and Best, a medical student, discovered insulin. Clinical investigators in hospitals such as this perfected the application of this new therapeutic agent

to clinical medicine, chemists produced the crystalline substance and developed other compounds, industry made them available by mass production, and millions of patients with diabetes and other equally serious ailments benefited. Drs. Minot and Murphy, both clinicians in the teaching hospitals of Boston, by discovering the effectiveness of liver in the treatment of pernicious anemia similarly contributed not only a specific therapy for a human ailment that had previously been fatal but also ideas that stimulated scientific work and provided opportunities for pharmaceutical endeavor that have been pursued efficiently. Fleming, working on the bacteriocidal property of tears, and Waksman, a soil bacteriologist, discovered, respectively, penicillin and streptomycin — therapeutic agents that have revolutionized medicine by reducing morbidity and mortality and that have resulted in expanding industrial activity and earnings. What does it matter whether these contributions are basic, biologic or applied science? For science is no end in itself. Their significance is that they are contributing to human health, wealth and happiness. Can the same be said of atomic energy, the latest contribution of basic science?

An extreme and puzzling example of the unique position of the clinical investigator and the teaching hospital arises in a consideration of how investigation of the prevention and treatment of mental disease will be advanced. Are we to rely on the basic sciences to break through the impasses that now confront us in this most distressing and costly field of medicine? Or should we support the clinical investigator, whose approach to the subject appears so unscientific to the scientist? I shall not attempt an answer, but shall venture the guess that the contributions that will ultimately open this field to scientific exploration will come from clinical investigators working with patients in teaching hospitals, not from basic scientists working in laboratories with mice or test tubes, or from the psychiatrists of overcrowded and underfinanced mental hospitals. The opportunities offered by the patients,

*Presented at a symposium "The Hospital in the Community" held during the Ether Day Centenary of the Massachusetts General Hospital, Boston, October 16, 1946.

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But to the extent that professional time and expense and the time of the patient can be saved without sacrificing necessary thoroughness and the personal relation, efficiency is gained. Medical group practice seems able to attain that end. Coordination of the patient's care is facilitated by staff organization, specialized facilities and unit case records. Hours of patient time and at least quarter-hours of doctor time are saved when special procedures or consultations are required. If these savings applied to only 15 per cent of cases, they would be important, but as noted above, the experience in New York suggests that a substantially higher proportion need the attention of a specialist. In addition, group practice reduces the expenses of the individual physician, practitioner and specialist alike, because facilities and ancillary personnel are shared. With everything taken into account, it is not an exaggeration to say that group practice can increase the efficiency of delivering medical services by 50 per cent.

Of course, no institution is better than the people who serve it, and medical-practice groups follow the rule. They do not guarantee a high standard of medicine, all they offer is a device to make good medicine easier to produce and cheaper to deliver. As such, they are key points in the reform of medical distribution.

The final requirement placed on reform is that it shall equitably apportion costs over the population. Health insurance is one method—voluntary or compulsory, or both. Direct taxation to raise the needed funds in whole or in part is still another method. But before any money is raised or insurance premiums are paid, the public should know precisely what is to be paid for and how the quoted cost was arrived at.

For example, a system of insurance that applied the methods and fees of the New York Workmen's Compensation Act to medical care for the population as a whole would raise the national health bill from four or four and a half billion to something over ten billion dollars. If, on the other hand, group practice were prevalent so that fixed-rate payments could be made to medical groups, the same quantity of service would cost only about seven billion dollars (I say "only" advisedly—the amount would still be less than that spent on automobiles).

It must immediately be said that these estimates cannot pretend to be precise, for experience with prepayment in this country is limited. At most, 10 per cent of medical costs are now paid through insurance, and the great bulk of that goes for hospitalization. Regarding professional services, experience is fragmentary and diverse—indicative but in no way conclusive.

In view of the paucity of experience, particularly the widespread ignorance of what medicine can and should be, the proposal to set up an all-inclusive, federal system of paying for medical care

seems premature. Although we may know enough to take the first strokes, it does not seem judicious to leap off the dock.

Nevertheless, it must be recognized that a large number of people in the United States cannot afford to pay, by themselves, for even the most efficiently delivered medical care. Whole areas now suffering from medical impoverishment cannot possibly support an adequate standard out of their own resources. It is unreasonable to suppose that these deficiencies can be made up without bringing the tax power into play. Medical care is surely an appropriate object of community expense, not only as a means of relieving suffering but also, even more, as a measure for raising the general capacities of the people. If properly expended, public monies disbursed for health services constitute an investment.

The art is to spend the funds properly. That we must learn, as we learn any art, by doing and closely observing the results. "*Far una prova*," the Italians call it—"to make a proof," rather than to wait for proof to arrive. Active experimentation at the local level is what is needed most.

It is pleasant to be able to report that New York is at work. The most notable attempt in this country to put into practice, on a community-wide scale, the concepts of medicine implied in this paper is the Health Insurance Plan of Greater New York, which, after more than two years of arduous preparation, should be in operation by the new year. But many similar attempts are needed throughout the Nation, and they should not be delayed. Only local knowledge gained by experience, as well as local understanding of what medicine is and can be, will ensure the delivery of good medicine in the future.

* * *

The restoration of medicine as a social institution to a state of equilibrium within itself is a job crying for the participation of the most highly qualified physicians. Thus far, leaders in the profession of medicine have taken an active part in only a few communities, leaders in the business of medicine have taken rather too great a part. Why is this not a subject for the medical schools? It is as much a matter of concern to medicine as foreign policy is to government. Statesmanship is needed, and where else should one look than to the medical schools?

What is required is the creation of a new discipline within medicine—it might properly be called "social medicine," which would concern itself with the relation of the medical arts and sciences to society. It is not a subject to be handled as an extracurricular activity at occasional institutes and conferences, it demands the same kind of concentrated attention and expertise as any major field of investigation and practice. Training in medical administration will not answer, useful though administrators would be, for something worth administering is necessary. Nothing less than organized

Scientific Research and Development — studies that systematically defined the efficient use, in the control and cure of malaria, of both the heretofore empirically used agents and the new and superior synthetic antimalarial drugs developed under this effectively planned and executed research program.

The experience obtained during these studies demonstrated again that the optimal utilization of medication in man can be defined only through clinical testing. The behavior of these drugs in the human being could not be predicted reliably from studies on animals other than the monkey. The same reservation is true of operating procedures. These studies also demonstrated the limitation even of the monkey owing to the difference between its susceptibility to disease and man's and to the difficulty of producing in the monkey the conditions simulating those demanding operative therapy in man. This does not mean that patients are used as guinea pigs. It means that teaching hospitals can give patients newer and more effective therapy than can be obtained elsewhere. Incidentally, it does not mean that as much information as possible should not be obtained on mice, rats, chicks, ducks, guinea pigs and other animals before studies are undertaken with the monkey. Only in that manner will the difficult and expensive monkey experiments be efficiently conducted, and will all the information be obtained that makes utilization of new drugs and operative procedure in man safe.

In this connection it may be remarked that the antivivisectionist is one of the few people who eat their cake and have it too. So long as he is unsuccessful in prohibiting such clinical investigation, he may safely indulge in denouncing that by which he happily benefits. For no doctor will give him a drug or subject him to an operation that has not been tried and perfected by experimentation.

Such development of new and better therapy is expensive. The O S R D studies on malaria therapy for two and a half years cost the Government some \$5,500,000. The clinical testing conducted by this hospital, which was one of five clinical testing units under the program, cost \$220,000. The total cost of the clinical testing probably approximated \$1,500,000. Yet had the war in the East lasted another year the reduction in the drug bill alone from the use of the new compounds instead of quinine and quinacrine would have paid for the studies. As it is, this saving will be realized by society in general, and a substantial profit will accrue to at least one pharmaceutical company.

The opportunity of similarly improving and developing therapy in other fields is wide open.

The field can best be cultivated not by collective farming but by the group services of teaching hospitals.

The effective utilization of these group services can be increased in other ways. For example, a paying patient rarely obtains the medical care that these group services are particularly qualified to give unless he is admitted to a hospital and occupies a hospital bed. Frequently this is unnecessarily confining and expensive and may deprive some other patient of the bed he really needs. The Mayo Clinic is, I believe, one of the few group practices that is equipped to make its hospital staff and laboratory facilities available to ambulatory patients.

One other consideration deserves mention because it may affect the future of the group services of teaching hospitals that — I hope we all agree — are fundamental to the improvement of medical care. If the current extension of medical, as differentiated from hospital, insurance is successful enough under either private or legislative plans to prevent illness itself from resulting in medical indigence, the services of the highly trained and integrated group practices of teaching hospitals may be curtailed. The patient who has heretofore come to the wards of such hospitals may for better or for worse elect to be cared for by an individual physician in either a teaching or a nonteaching hospital. The problem that this presents is not dependent on the extension of governmental insurance. As a matter of fact, the legislative proposals, except so far as they may be more successful in covering more people, present less threat in this respect than the voluntary schemes. They permit the patient free choice of a physician, groups of physicians or hospitals, whereas the voluntary schemes provide for free choice only of a physician. The legislative proposals also make provision for financing medical teaching and research. The voluntary plans do not.

Such a possible effect of extension of medical insurance does not indicate, I trust, that indigence must be perpetuated in the interest of improving medical care. It does mean, however, that, if the group services of teaching hospitals are to weather the critical years ahead, they must be strengthened by increasing the public's understanding and appreciation of the services they render. It means that we must, in a business-like manner, assure payment for the benefits society receives. Let us consider the means of doing these things without prejudice and in the light of what is best for the public as a whole solve the problems and take advantage of the opportunities to develop the teaching general hospital to its full potentialities.

staff and research facilities of this hospital, with its department of psychiatry in intimate association with every division of this general hospital and with the McLean Hospital, were thoughtfully conceived and are being well pursued. But the personnel of both that department and the McLean Hospital are inadequate — inadequate in terms of diversity of training, number and especially time free of the overwhelming demand for the meager therapy that is available today.

A teaching hospital not only provides the facilities essential to clinical investigation but also develops groups of investigators that are larger and more enduring in life, though not in memory, than the individual. These groups, led by the Churchills, Meanses, Cobbs, Aubs, Bauers, Albrights, Whites and others, are continually working for all of us and our children not only by their contributions to new and better medicine but also by educating you and all physicians and by caring for patients. They largely provide the stock in trade of medical care that your good doctors sell you. They teach the medical student, the intern, the resident, the graduate fellow and the postgraduate physician. They give the lectures at medical-society meetings and write the articles in medical journals. They determine the quality and the nature of the medicine of tomorrow. In doing this they are the best salesmen of pharmaceutical products. And while doing this they are personally giving all of us, day and night, the special care that they, through this institution, are particularly equipped to give.

What is the public's and industry's and your appraisal of the worth of such service? Compare the salaries and equipment of hospitals with those of industry serving society by developments pertaining to automobiles, airplanes, agricultural implements, radios, rubber, plastics and chemotherapeutic agents. Salaries of \$2,000 to \$4,500 are usually paid clinical investigators. The provision of more is difficult. Moreover, appointment is usually on a short-term basis, and too frequently a salary is dependent on a year's grant whose renewal may not be determined until two weeks before its expiration date. There are several men in this room whose contributions to medical knowledge have made them known in every country in the world that enjoys the benefit of modern medical science. They get just such salaries. The technical workers in clinical laboratories — college graduates and highly skilled persons — fare no better, receiving salaries of from \$1,500 to \$2,000 as compared with the \$2,000 to \$3,000 available to them in industry. Yet clinical research depends in no little degree on the quality of their work. And the quality of medical care depends more and more on the information that such technicians give physicians or surgeons concerning the composition of the blood, its type, the micro-organism that is involved or the tumor that is or is not malignant.

One wonders if the pharmaceutical companies are wise in putting more money into advertising than into the hospitals that introduce their products and educate doctors in their use.

Is it because the charity tradition still pervades the public's concept of the large teaching urban hospital that the public, in making payments under hospital and medical-insurance plans, does not pay costs and thus still leaves much to charity? Does that tradition, as well as the educational character of these hospitals, encourage sentimental support rather than a realistic and material purchase of the concrete services rendered? We speak of supporting hospitals but not of supporting industries. Each of us buys what he gets. Perhaps the inadequate support of hospitals reflects the thought that medicine is concerned with lessening illness rather than producing health — the value of the institution, therefore, being conceived of in negative rather than positive terms. Yet people spend literally billions on doctors and pills. Medicine is, I believe, the third largest business in terms of money spent. But the teaching hospital, which determines in no small way the quality and improvement in medical care, is faced with possible bankruptcy. A past president of the American Hospital Association, who knows hospitals, remarked at a meeting a few months ago that there were probably only a dozen hospitals in the United States that would avoid insolvency in the next few years unless there is a drastic change in hospital financing. If the public does not finance the difference in the cost of medical care given by such institutions as this and that given by the smaller hospital, how can the teaching hospital continue to provide the difficult medical care for which doctors refer patients to obtain the treatment that is not available elsewhere? It is that type of care that makes the value of this institution, both to the patients who come here and to all those who never come here but who benefit by the doctors, nurses, social workers, dietitians and technicians who are educated here. It is the new, the carefully controlled and the well defined therapy that such hospitals as this provide that makes them of value to industry.

They could be made of far more value. The most effective utilization of a therapeutic agent demands at least a knowledge of its absorption and distribution within the body, of its excretion and degradation and of its toxicity and therapeutic effectiveness in relation to concentration in body fluids and tissues. This information has been obtained for only a few of all the many therapeutic compounds used today. One may well ask if we are administering such generally used substances as the barbiturates, hydantoins and digitalis preparations to no better advantage than we used quinine and quinacrine prior to the recent studies conducted under the direction of the Board for Co-ordination of Malaria Studies of the Office of

pressed the bulk of the cut surface was frankly red and of a distinctly soft consistence. Close scrutiny of these areas revealed a completely collapsed and considerably disintegrated architecture of the liver lobules. The entire gross picture, therefore, was interpreted as showing a marked degree of acute atrophy of the liver in what might be termed a predominantly "red" rather than a "yellow" state.

The histologic picture, as revealed in several different sections, showed extensive liver damage of a decidedly acute nature (Fig. 2). There were marked necrosis and destruction of the liver-cord cells and, over large areas, complete collapse

The gall bladder was of normal size and thin walled and contained no calculi. Its fundus protruded almost 4 cm. beyond the upper edge of the markedly atrophic liver. The extrahepatic biliary passages were collapsed and contained only a slight amount of thin yellow bile.

The spleen was of average size, weighing 160 gm., and was grossly not remarkable. Microscopically there was marked atrophy of the malpighian follicles. There was also considerable congestion of the red pulp with dilatation of the sinusoids, which contained moderate numbers of leuko-

TABLE 1 Significant Laboratory Data

DATE	FASTING BLOOD GLUCOSE mg/100 cc	BLOOD UREA NITROGEN mg/100 cc	SERUM PHOSPHORUS mg/100 cc	SERUM BILIRUBIN mg/100 cc	TOTAL PROTEIN gm/100 cc	SERUM ALBUMIN gm/100 cc	SERUM GLOBULIN gm/100 cc
1/26/45	56	11	—	19.2	6.1	—	—
1/27/45	86	—	5.4	—	5.1	2.4	2.7
1/29/45	62	15	4.8	25.0	6.1	2.8	3.3

of the normal architecture. In these collapsed areas the lobular pattern had entirely vanished, there remained only scattered regressive liver cells singly and in disjointed groups within the condensed and inflamed stroma (Fig. 3). Many of the necrotic and necrobiotic liver cells contained a great deal of fine, granular, golden pigment, apparently bilirubin or lipofuscin. In addition, there was distinct proliferation of the bile ducts, as well as considerable swelling of fixed tissue cells. Numerous lipid-laden histiocytes were found, and there was much acute inflammatory infiltration, particularly in the periportal areas. Many bile canaliculi and a few smaller bile ducts were distended with bile thrombi. Other small bile ducts contained neutrophilic exudate within their lumens. In the more severely damaged areas there remained only small isolated groups of apparently undamaged liver

cytes and plasma cells, in addition to erythrocytes. The reticulum was slightly increased.

The kidneys were of average size, with thin, easily removable capsules. Aside from minimal persistence of embryonal lobulation they presented only slight diffuse, fine granular

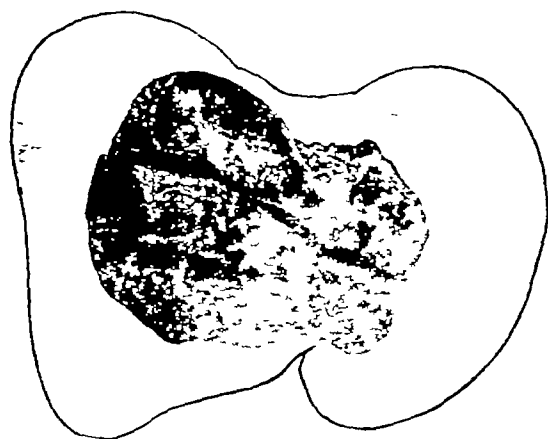


FIGURE 1 Photograph of the Liver
The outline indicates the size of a normal liver

cords. Finally, the preserved areas described grossly revealed fair-sized, intact remnants of liver parenchyma. Here, there was considerable edema of the intervening sinusoids, which were exceedingly dilated and filled with granular detritus. The liver cells, although intact, showed distinct regressive changes, with vacuolization and granularity of the cytoplasm. Here, too, were occasional necrobiotic and necrotic parenchymatous cells, whereas the bile canaliculi showed numerous bile thrombi. The over-all histologic picture was that of a severe degree of acute toxic necrosis, such as that seen in acute yellow atrophy.

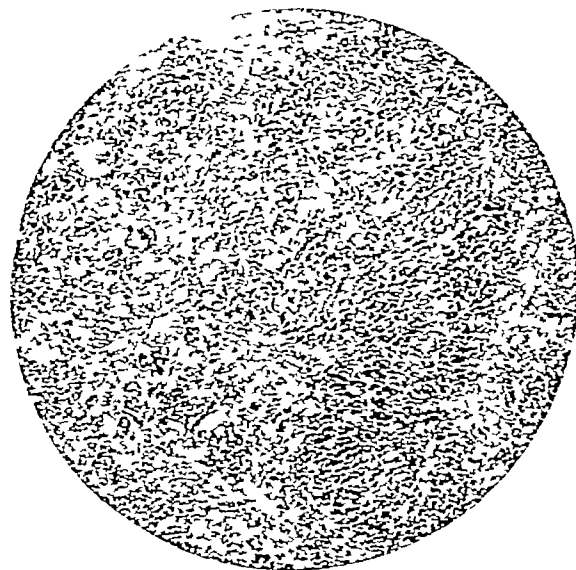


FIGURE 2 Photomicrograph of the Liver
This shows a remnant of parenchyma with marked inflammatory reaction in the periportal stroma and proliferation of the bile ducts

scarring of the cortices. On section the parenchyma revealed distinct icterus, a regular corticomedullary junction and a cortex of about 7 mm in thickness. The major renal vessels, the pelves and the ureters were not remarkable. The urinary bladder was completely contracted and contained only a few drops of urine.

Microscopical sections of the kidneys revealed interesting findings. Aside from a rare hyalinized glomerulus, the renal corpuscles were entirely intact. Occasionally, the glomerular spaces were slightly dilated and contained droplets of deep-pink-staining material.

The tubular system, however, showed severe alterations

ACUTE YELLOW ATROPHY FOLLOWING CINCHOPHEN ADMINISTRATION*

Report of a Case

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ABOUT twenty years ago Cabot¹ first reported a case of acute yellow atrophy allegedly due to cinchophen. Although similar cases have been recognized since that time, clinicians who use cinchophen with no observed untoward effects have minimized it as a hepatotoxic agent. One series has been reported, for example, in which cinchophen was given to 2500 patients without a fatal case.²

The toxic manifestations of cinchophen against which the physician is usually cautioned are chiefly those of the skin. Among them, urticaria and the erythematous morbilliform rashes are said to be most frequently encountered. But perhaps more important are signs indicative of hepatic damage. These include nausea, emesis, dark urine, icterus and discomfort in the right upper quadrant. With these symptoms the dermatologic complaint is, unfortunately, an infrequent one.

The following case of acute yellow atrophy terminated fatally twelve days after the ingestion of 2 gm of cinchophen.

A 59-year-old Jewish housewife was admitted to the surgical service of Dr. Herbert A. Smith with the chief complaints of painless progressive jaundice, anorexia and nausea of 6 days' duration. The first symptoms had been extreme anorexia and nausea, without emesis or abdominal discomfort. These were accompanied by jaundice and dark urine, both of which had deepened rapidly. Two days after the onset of these initial symptoms, an attempted gall-bladder visualization had failed. Fluoroscopy with roentgenograms had disclosed no abnormalities of the esophagus, stomach, duodenum or abdomen. Continued nausea had prevented food intake of any consequence almost from the onset. Listlessness had progressed to drowsiness, and fleeting episodes of disorientation had become evident on the day preceding admission.

The patient had seen a physician for a long-standing arthritis of the ankles. She had taken a total of 2 gm of cinchophen on the day preceding the onset of the initial symptoms. So far as could be determined from her physicians and family, cinchophen had not been given previously.

The past history revealed that during the preceding 4 years the patient had been receiving salicylates and injections of vaccine, as well as physiotherapy for the ankles. These measures had been instituted by several physicians for rheumatoid arthritis. She had always been ambulatory. Since for 1 year before admission she had experienced mild postprandial eructations and because of obesity, fatty foods had been eliminated from the diet. The eructations had been relieved, and the weight remained constant. There had been no change in bowel habits. Twenty-three years previously, vaginal hysterectomy had been performed under ether anesthesia for a fibroid uterus. There was no history of previous icterus or of transfusions.

Physical examination at the time of admission disclosed a moderately obese, somewhat disoriented woman with a deeply bronzed icterus. The pupils were regular, equal and normally reactive, neurologic survey revealed no abnormalities. There were no tophi. The tongue was somewhat dry, and the mucous membranes icteric. The heart and lungs were not remarkable. Neither the liver nor the spleen was palpable or tender. Rectal examination was negative. Rheumatoid arthritis of the ankles was present. The blood pressure was 150/80, the temperature, pulse and respirations were normal.

The results of certain laboratory procedures are presented in Table 1. The serum alkaline phosphatase was 7.3 Bodansky units per 100 cc. A cephalin flocculation test was + + + +, and the prothrombin time, 30 seconds (normal, 16 seconds). Urinalysis revealed a few red and white cells, a positive test for bile in a dilution of 1:100 and a specific gravity of 1.014; there was no albumin on admission, but a + test was obtained on the following day. The stool was tan gray. The blood film showed a uniformly, mildly macrocytic picture. Examination of the blood revealed a red-cell count of 4,500,000, with 13.5 gm of hemoglobin (photometric—normal, 14.4 gm). The hematocrit reading was 49 on the same sample of blood. The mean corpuscular volume of the erythrocytes, therefore, was 109 cubic microns. The white-cell count was 7000 on admission, and 17,000 on the fourth hospital day, 70 per cent of the leukocytes were neutrophils.

The course was rapidly downhill. Drowsiness and disorientation progressed to semicomatose by the 2nd hospital day. Severe, irreversible hepatic damage was present, as evidenced by the cholemic state and by a definite decrease in the size of the liver to percussion on successive examinations. The plasma prothrombin time remained elevated to 30 seconds even after the administration of menadione bisulfite. No ecchymoses were observed at any time.

It was decided to give a massive dose of methionine intravenously. Accordingly, 15 gm of crystalline *D,L* methionine (0.25 gm per kilogram of body weight) was dissolved by boiling in 500 cc of a 10 per cent solution of casein hydrolysate. This was infused without reaction over a period of 4 hours. The natural course of the disease progressed unaltered, however. Despite adequate parenteral fluids, oliguria was noted on the following day. Coma deepened, and the atmosphere in the patient's room soon became permeated with a peculiar, musty odor, not unlike that of the infused methionine solution. Signs of free peritoneal fluid developed, in addition to those of bronchopneumonia, and the patient died on the 4th hospital day—12 days after the jaundice and dark urine had first been noticed.

Autopsy. The body was that of a moderately proportioned woman measuring 147 cm in length. The integument and conjunctivae exhibited deep icterus. There was no peripheral edema. Exposure of the peritoneal cavity revealed 1500 cc of brown-yellow ascitic fluid. An unusually atrophic liver (Fig. 1) lay considerably recessed beneath the right costal margin. Its surface was irregular, with low, plateau-like, tawny-brown elevations separated by rather extensive, irregularly shaped, depressed deep-red areas. The organ weighed 650 gm (normal weight, 1200 to 1400 gm).

The cut surface of the liver presented a striking picture. Only a few portions of the parenchyma remained intact. The largest sections, which were situated chiefly in the superior portion of the right lobe beneath the capsule and also in the caudate lobe, varied in size from that of a large cherry to that of a walnut. In the left lobe there were a few much smaller remnants varying from match-head to pea size. All these remnants were grossly green yellow, suggesting icterus and considerable fatty change. There were no structures that could be interpreted grossly as nodular regenerates. The intervening tissue, which com-

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all of which autopsy was performed, — noted in every case that there was evidence of a "hepatitis" or of a "degeneration" of the parenchyma of the liver. Each of his own cases exhibited a toxic cirrhosis after a terminal hepatic illness of several weeks' duration.

It is of interest to compare certain of the histologic findings in the case presented above with those observed by Lucké⁴ in his study of fatal epidemic hepatitis. In our case, in which there was no appreciable zonal pattern of destruction in the liver lobule, such as that described in epidemic hepatitis, the agent apparently attacked all regions within the lobule with equal severity, producing all stages of cellular disintegration — fatty changes, vacuolization and coagulation of cytoplasm — and cellular death. This pattern of necrobiosis and necrosis, in itself, also differs from that observed in fatal epidemic hepatitis, in which rapidity and completeness of cell destruction are distinguishing features.⁴ In the regions still intact, however, the inflammatory infiltration was more marked in the periportal areas, consisting largely of neutrophils.

We observed no endophlebitis of the central veins. Nor was there any recognizable persistence of the outline, by small proliferating bile ducts, of the completely destroyed lobules. Both features were described in epidemic hepatitis. A characteristic of acute yellow atrophy that was well shown in this case was the extraordinarily rapid disappearance of many of the damaged liver cells. Lucké, also noting this phenomenon in his material, assumed that the necrotic cells had been swept away by enzymatic action. The tempo of the disease in our patient was apparently of such rapidity as to preclude the development of nodular regenerates.

Recently, studies on acute or fulminant epidemic hepatitis running a fatal course in ten days or less have appeared.^{5,6} In most cases the liver presented a moderate reduction in size, with a smooth or occasionally finely wrinkled surface. Nodular regeneration, prominent in the subacute form of this disease, was absent or minimal. Microscopically, extensive destruction of liver cells dominated, usually involving uniformly all parts of the liver. Apparently, this occurred initially in the central zones of the lobule. Even in cases with a clinical history of brief duration, cell destruction was often far advanced, and complete lobules had been swept away. Inflammatory reaction, most conspicuous at the lobular periphery, was severer than that in the subacute form of the disease.

The case presented above, however, differs in certain respects from fulminant epidemic hepatitis, notably in the size and shape of the liver, the gross appearance of the cut surface and certain microscopical findings, such as the presence of stages of cellular degeneration and the absence of zonal patterns of disintegration.

So far as the cause of the hepatic damage is concerned, can the administration of cinchophen be considered merely an unfortunate coincidence? The report by Palmer and Woodall⁷ of 88 deaths in 191 recorded cases of hepatitis associated with cinchophen seems sufficient clinical proof for the hepatotoxic potentialities of this drug in the susceptible patient. MacBryde⁸ states that a number of cases of toxic hepatitis consequent to cinchophen undoubtedly have been mislabeled acute infectious hepatitis. Frequently, as in the case presented above, a history of cinchophen ingestion is not elicited at the initial inquiry.

It has been observed that cholemic nephrosis has received much less attention than the condition merits.⁴ Fahr⁹ described the findings in cholemic nephrosis in some detail in 1925. Ayer's¹⁰ pathological analysis of renal lesions in 18 infants who were jaundiced from congenital biliary atresia is perhaps more comprehensive than any written about this lesion. He consistently found pigmented bile casts in the distal convoluted and collecting tubules in his cases.

In a subsequent study of post-transfusion uremia, Ayer and Gauld¹¹ concluded that the essential features of the renal lesions following fatal transfusion reactions were similar to those seen in the kidneys of infants with biliary atresia. The findings in the kidneys of patients succumbing to subacute epidemic hepatitis also correspond to those described by Ayer.

The tubular lesions seen in our patient also closely paralleled those reported by Ayer in jaundiced infants. Not heretofore described, however, in the nephroses accompanying acute yellow atrophy, acute or subacute epidemic hepatitis, obstructive jaundice or post-transfusion uremia is the presence of a considerable amount of calcium in the cortical collecting tubules and their peripheral branchings and also within occasional distal convolutions. Flocks¹² recently reported asymptomatic pelvic and intrarenal calcium urolithiasis in its early stages. Although its exact intrarenal location is not described, — except within the tubules, — it is presumably located within the collecting tubules and ducts of Bellini in the pyramids. Flocks termed the substance a "phosphate."

What is the mechanism of this calcium precipitation? Several possible causes can be excluded. So far as we were able to determine, the patient had never taken irradiated ergosterol. Except for short periods she had been ambulatory, hypercalcaemia due to osteoporosis from immobilization being thus eliminated. At autopsy the parathyroid glands were not conspicuous, nor were there any evidences of multiple myeloma. Urinary stasis, infection and heavy metal intoxication were also absent.

It seems then, that few possibilities remain. So far as we know, the infused methionine solution did not contain significant amounts of calcium salts.

The proximal parts of the collecting ducts exhibited marked albuminous degeneration with a great deal of concentric debris and droplets of eosinophilic material within the lumen.

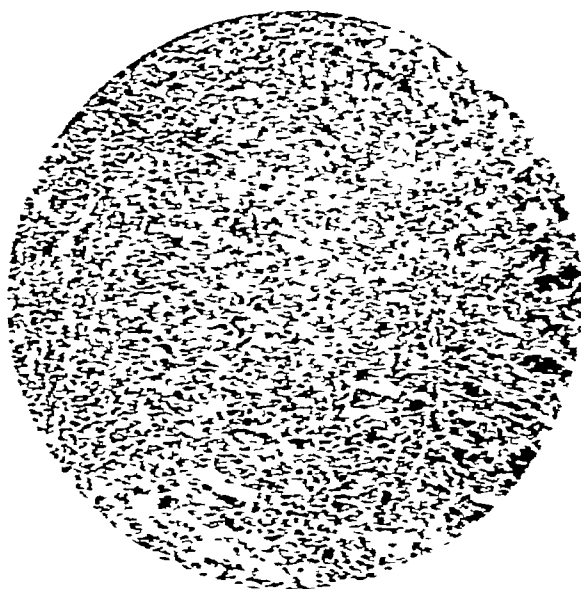


FIGURE 2. Photomicrograph of the Liver.

It is a cross-section of a collecting duct of the liver showing eosinophilic material within the lumen.

Most of the thin segments were dilated and empty, but a few contained eosinophilic casts. The ascending limbs of Henle's loops occasionally contained similar casts and

appeared. Occasionally, cystic structures were seen—probably dilated convolutions of collecting ducts—lined by flattened epithelium. These contained a similar eosinophilic granular substance.

Perhaps most interesting were the lesions in the collecting tubules. The peripheral portions of the collecting ducts showed rather ordinary dilated lumens with numerous flat cells. Many of the collecting tubules in the connective portions of the medullary rays contained considerable amounts of a peculiar amorphous granular material similar to the noted in the duct convolutions. This substance, taking a dark bluish-gray color in a hematoxylin-eosin preparation, gave a positive reaction with the von Jaksch stain for cholesterin (Fig. 3). With this reaction it was apparent that although the bulk of this material lay within the lumen, small amounts were deposited in the cytoplasm of the tubular epithelium as well.

The small capillary vessels of the stroma showed minor hyperemia, especially in the pyramids. The small arteries revealed moderate elastic thickening.

Both lower lobes of the lungs grossly showed diffuse alveolar emphysema with slight to moderate hyperemia in

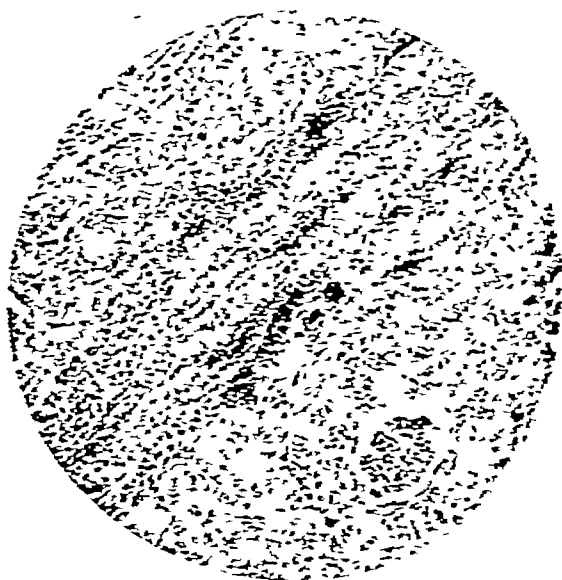


FIGURE 3. Photomicrograph of a Kidney.

The section shows a dilated collecting duct of the kidney with eosinophilic material within the lumen.

hemorrhage, some of the alveolar parenchyma. Histologic sections showed marked signs of recent pneumonia.

The heart was of normal size and grossly revealed entirely normal chambers, valves and coronary arteries. Histologically, the myocardium showed only slight interstitial edema with scattered plasma cells and leukocytes, and distinct edema swelling of the myocardial bundles.

All other organs, including the pancreas and the thyroid, parathyroid and adrenal glands, were normal. Permission was not granted for examination of the brain.

The findings in the liver in this case correspond well with the classic pathological picture of an acute toxic necrosis. That the disease was of a fulminating character clinically is amply shown pathologically by the severity of parenchymatous damage, the acute inflammatory response and the absence of regeneration or of reactive fibrosis. Reichle,³ in a review of 7 reported cases of death due to cinchonism, to which he added 2 cases of his own—in

many a bile collector. Bile casts which were more frequent in the ductal convolutions, were rarely associated with 1 or 2 mononuclear cells within the lumen (Fig. 4). In several distal convoluted tubules a dark-blue granular substance

FIGURE 4. Photomicrograph of a Kidney.

This is a cross-section of a dilated collecting duct of the kidney showing eosinophilic material within the lumen.

all of which autopsy was performed, — noted in every case that there was evidence of a "hepatitis" or of a "degeneration" of the parenchyma of the liver. Each of his own cases exhibited a toxic cirrhosis after a terminal hepatic illness of several weeks' duration.

It is of interest to compare certain of the histologic findings in the case presented above with those observed by Lucké⁴ in his study of fatal epidemic hepatitis. In our case, in which there was no appreciable zonal pattern of destruction in the liver lobule, such as that described in epidemic hepatitis, the agent apparently attacked all regions within the lobule with equal severity, producing all stages of cellular disintegration — fatty changes, vacuolization and coagulation of cytoplasm — and cellular death. This pattern of necrobiosis and necrosis, in itself, also differs from that observed in fatal epidemic hepatitis, in which rapidity and completeness of cell destruction are distinguishing features.⁴ In the regions still intact, however, the inflammatory infiltration was more marked in the perportal areas, consisting largely of neutrophils.

We observed no endophlebitis of the central veins. Nor was there any recognizable persistence of the outline, by small proliferating bile ducts, of the completely destroyed lobules. Both features were described in epidemic hepatitis. A characteristic of acute yellow atrophy that was well shown in this case was the extraordinarily rapid disappearance of many of the damaged liver cells. Lucké,⁴ also noting this phenomenon in his material, assumed that the necrotic cells had been swept away by enzymatic action. The tempo of the disease in our patient was apparently of such rapidity as to preclude the development of nodular regenerates.

Recently, studies on acute or fulminant epidemic hepatitis running a fatal course in ten days or less have appeared.^{5, 6} In most cases the liver presented a moderate reduction in size, with a smooth or occasionally finely wrinkled surface. Nodular regeneration, prominent in the subacute form of this disease, was absent or minimal. Microscopically, extensive destruction of liver cells dominated, usually involving uniformly all parts of the liver. Apparently, this occurred initially in the central zones of the lobule. Even in cases with a clinical history of brief duration, cell destruction was often far advanced, and complete lobules had been swept away. Inflammatory reaction, most conspicuous at the lobular periphery, was severer than that in the subacute form of the disease.

The case presented above, however, differs in certain respects from fulminant epidemic hepatitis, notably in the size and shape of the liver, the gross appearance of the cut surface and certain microscopical findings, such as the presence of stages of cellular degeneration and the absence of zonal patterns of disintegration.

So far as the cause of the hepatic damage is concerned, can the administration of cinchophen be considered merely an unfortunate coincidence? The report by Palmer and Woodall⁷ of 88 deaths in 191 recorded cases of hepatitis associated with cinchophen seems sufficient clinical proof for the hepatotoxic potentialities of this drug in the susceptible patient. MacBryde⁸ states that a number of cases of toxic hepatitis consequent to cinchophen undoubtedly have been mislabeled acute infectious hepatitis. Frequently, as in the case presented above, a history of cinchophen ingestion is not elicited at the initial inquiry.

It has been observed that cholemic nephrosis has received much less attention than the condition merits.⁴ Fahr⁹ described the findings in cholemic nephrosis in some detail in 1925. Ayer's¹⁰ pathological analysis of renal lesions in 18 infants who were jaundiced from congenital biliary atresia is perhaps more comprehensive than any written about this lesion. He consistently found pigmented bile casts in the distal convoluted and collecting tubules in his cases.

In a subsequent study of post-transfusion uremia, Ayer and Gauld¹¹ concluded that the essential features of the renal lesions following fatal transfusion reactions were similar to those seen in the kidneys of infants with biliary atresia. The findings in the kidneys of patients succumbing to subacute epidemic hepatitis also correspond to those described by Ayer.

The tubular lesions seen in our patient also closely paralleled those reported by Ayer in jaundiced infants. Not heretofore described, however, in the nephroses accompanying acute yellow atrophy, acute or subacute epidemic hepatitis, obstructive jaundice or post-transfusion uremia is the presence of a considerable amount of calcium in the cortical collecting tubules and their peripheral branchings and also within occasional distal convolutions. Flocks¹² recently reported asymptomatic pelvic and intrarenal calcium urolithiasis in its early stages. Although its exact intrarenal location is not described, — except within the tubules, — it is presumably located within the collecting tubules and ducts of Bellini in the pyramids. Flocks termed the substance a "phosphate."

What is the mechanism of this calcium precipitation? Several possible causes can be excluded. So far as we were able to determine, the patient had never taken irradiated ergosterol. Except for short periods she had been ambulatory, hypercalciuria due to osteoporosis from immobilization being thus eliminated. At autopsy the parathyroid glands were not conspicuous, nor were there any evidences of multiple myeloma. Urinary stasis, infection and heavy metal intoxication were also absent.

It seems then, that few possibilities remain. So far as we know, the infused methionine solution did not contain significant amounts of calcium salts.

The proximal convolutions exhibited marked albuminous degeneration with a great deal of desquamated detritus and droplets of deep-pink-staining material within the lumen

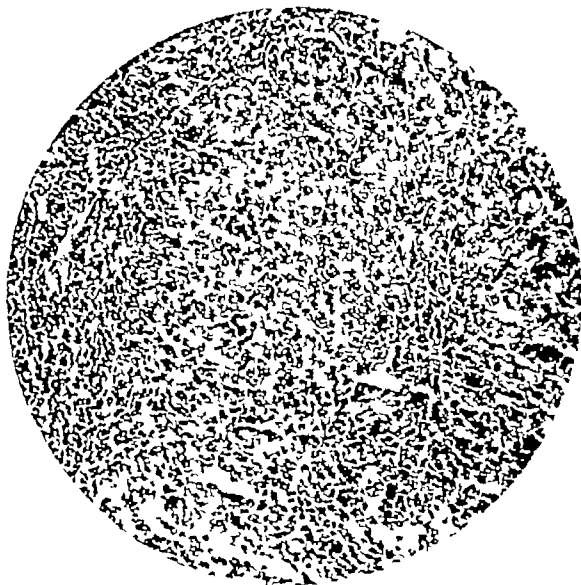


FIGURE 3 Photomicrograph of the Liver

In the remnant of parenchyma there are regressive changes and vacuolization in the cytoplasm of the liver cells, as well as an inflammatory reaction in the sinusoids and the periportal stroma

Most of the thin segments were dilated and empty, but a few contained red-pink-staining casts. The ascending limbs of Henle's loops occasionally contained similar casts, and

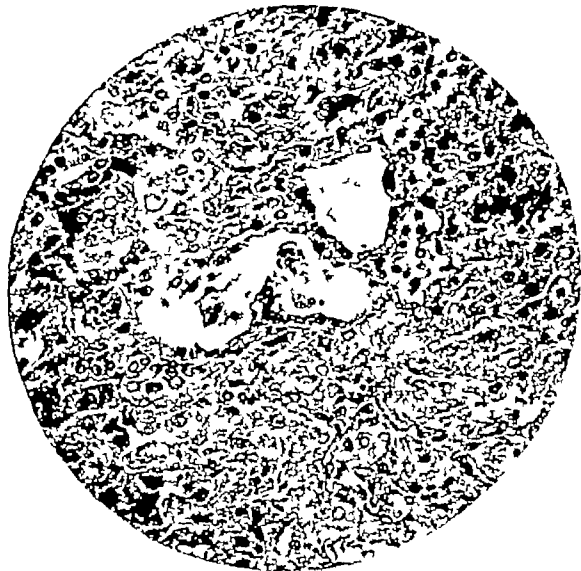


FIGURE 4 Photomicrograph of a Kidney

Note the dilatation of a distal convoluted tubule, with bile cylinders and mononuclear cells within the lumen

rarely a bile cylinder. Bile casts, which were more frequent in the distal convolutions, were rarely associated with 1 or 2 mononuclear cells within the lumen (Fig 4). In several distal convoluted tubules a dark-blue granular substance

appeared. Occasionally, cystic structures were seen—possibly distal convolutions or collecting ducts—lined by flattened epithelium. These contained a similar dark-blue granular substance.

Perhaps most interesting were the lesions in the collecting tubules. The peripheral branchings of the collecting ducts showed rather distinctly dilated lumens with numerous bile cylinders. Many of the collecting tubules in the centrifugal portions of the medullary rays contained considerable amounts of a peculiar, amorphous, granular material similar to that noted in the distal convolutions. This substance, taking a dark bluish-purple color in a hematoxylin-eosin preparation, gave a positive reaction with the von Kossa stain for calcium (Fig 5). With this technic it was apparent that although the bulk of this material lay within the lumen, small amounts were deposited in the cytoplasm of the tubular epithelium as well.

The small capillary vessels of the kidneys showed intense hyperemia, especially in the pyramids. The small arteries revealed moderate sclerotic thickening.

Both lower lobes of the lungs grossly showed distinct flaccid atelectasis, with slight to moderate, apparently in-



FIGURE 5 Photomicrograph of a Kidney

This section shows deposits of calcium in the collecting tubules of the medullary rays (von Kossa stain)

flammatory, edema of the atelectatic parenchyma. Histologic sections showed marked signs of recent pneumonia.

The heart was of normal size and grossly revealed entirely normal chambers, valves and coronary arteries. Histologically, the myocardium showed only slight interstitial edema, with scattered plasma cells and leukocytes, and distinct cloudy swelling of the myocardial bundles.

All other organs, including the pancreas and the thyroid, parathyroid and adrenal glands, were normal. Permission was not granted for examination of the brain.

The findings in the liver in this case correspond well with the classic pathological picture of an acute toxic necrosis. That the disease was of a fulminating character clinically is amply shown pathologically by the severity of parenchymatous damage, the acute inflammatory response and the absence of regeneration or of reactive fibrosis. Reichle,³ in a review of 7 reported cases of death due to cinchophen, to which he added 2 cases of his own, — in

LEUKEMIA CUTIS*

Report of a Case, with a Discussion of Treatment by the Use of Hormones

WILLIAM H. ROBEY, M.D.,† AND G. GARDINER RUSSELL, M.D.‡

BOSTON, MASSACHUSETTS, AND HARTFORD, CONNECTICUT

LEUKEMIA is characterized by hyperplasia of the leukopoietic tissues throughout the body and is usually associated with qualitative and quantitative variations in the circulating leukocytes. *Urticaria*, *pruritus* and *prurigo*, hematomas and actual tumor formations may occur. In the case reported below, the intense skin involvement began early, the leonine appearance of the face and general leukemic infiltration of the skin led to the diagnosis of leukemia cutis—a rare manifestation, only 4 cases having been seen at the Boston City Hospital in twenty years. In association with these skin lesions the blood may remain normal for years or may show only slight changes. Two biopsies early in the disease showed the leukemic lymphocytic infiltration of the lesions.

The case is reported because of its rarity and the effect of hormones on the subjective and objective symptoms.

C. W. P., a 51-year-old married business executive, had always enjoyed perfect health, his habits were excellent, and he kept good hours and used alcohol and tobacco in great moderation.

Late in March, 1942, a slight rash appeared, first on the chest and then on the upper back. No discomfort was felt, nor was there any indisposition. Two or three weeks later, a mild itching developed, increasing sufficiently to interfere with sleep. Gradually, the pin-point spots became confluent, emerging into larger and larger areas until the whole trunk took on the appearance of a mild sunburn. About the middle of June, there was a sharp attack of diarrhea of approximately 12 hours' duration that the patient attributed to food poisoning. A day or so later he noticed a slight swelling of some of the superficial lymph nodes and consulted one of us (G. G. R.).

The itching, especially at night, was increasing but not enough to interfere with the patient's daily activities. The lymph nodes seemed to subside, and there was little change for several weeks. On July 26, the patient played two rounds of golf, which he thoroughly enjoyed, and did not feel fatigued. Two days later, however, he was rather stiff and concluded that his game had brought into play some muscles not recently used. On the following day there was some swelling of the lymph nodes in the groins and axillae. His physician then made a complete physical examination that was stated to be negative, except for the skin and lymph nodes.

Three days later the nodes had increased in size, and the color of the skin had deepened. On August 3 a biopsy was performed, and 6 days later the patient was admitted to the Thorndike Memorial Laboratory, Boston City Hospital, where these clinical findings were confirmed by Drs. W. B. Castle and T. H. Ham. Of particular interest were the raised, nodule-like and hyperkeratotic plaques and the enlargement of the lymph nodes in the submental, cervical, axillary and inguinal areas. The nodes were approximately 1 cm. in diameter, elastic, movable and only occasionally slightly tender. There was doubt about enlargement of the spleen.

Examination of the blood on several occasions disclosed a white-cell count of 9000 to 9600, with 36 per cent adult and 5 per cent band neutrophils, 1 per cent eosinophils, 22 per cent small, 19 per cent large, 8 per cent young and 6 per cent atypical lymphocytes and 3 per cent adult monocytes. The red-cell count was 4,600,000, and on a smear the red cells and platelets appeared normal. The small, young and abnormal lymphocytes had nucleoli, but the cytoplasm did not appear immature. The sedimentation rate was normal, as was an x-ray film of the chest.

The most important diagnostic problem was the interpretation of the biopsy. Dr. Frederic Parker, Jr., did not come to a conclusion on the skin biopsy but made the following comment on that of the lymph node:

The lymph node shows a loss of normal structure for the most part. It is diffusely infiltrated with what appear to be adult lymphocytes. The infiltration also extends into the surrounding tissues. Mitotic figures are fairly numerous. The most probable diagnosis seems to be lymphocytoma, which is consistent with lymphatic leukemia in either the aleukemic or the leukemic phase.

The diagnoses considered were leukemia cutis, Hodgkin's disease of the skin and mycosis fungoides in an early stage. Everything, however, seemed to point to one diagnosis: lymphatic leukemia of the skin, with diffuse erythematous thickening and pruritus, enlargement of the lymph nodes and moderate alteration of the differential count of the blood. A hope was expressed that the course of the disease would be sufficiently slow to permit reasonable comfort and the ability to work.

The proposed treatment consisted of x-radiation of the skin and lymph nodes and the use of Navitol as well as sunlight. Since it was known that some of these cases have been aided greatly by massive doses, the patient was given initially 20 drops of Navitol three times a day and finally 120 drops a day. It was suggested that this treatment be given a trial of from 6 weeks to 3 months with the hope of less itching and possibly some clearing of the lesions. If the Navitol did not help, it might be discontinued and given a trial after a month. Sunlight was to be tried over one area, namely the back, in direct exposure for 10 minutes, the time being increased 5 minutes every other day until there was an opportunity to observe if the area tanned and if the itching was relieved.

On September 29, the patient had taken Navitol in full dosage for 10 days. The skin was becoming a deeper red, more pruritic and in some areas more indurated. The superficial pelvic lymph nodes were more prominent, and a small amount of edema of the feet was observed. Examination of the blood revealed a red-cell count of 3,980,000, with a hemoglobin of 13 gm. (85 per cent), and a white-cell count of 20,450, with 17 per cent neutrophils, 81 per cent normal and abnormal lymphocytes and 2 per cent eosinophils, some of the lymphocytes appeared young. The skin discomfort was more intense. Small doses of Dilaudid probably lessened the itching somewhat and therefore diminished insomnia.

In spite of the x-ray therapy and the doses of Navitol, the patient's discomfort continued to mount, the itching became more constant and violent, the lymph nodes larger and the skin more indurated, and in addition the scrotum and penis were markedly edematous. It was decided to send the patient to the Memorial Hospital in New York City, where he was studied by Drs. C. P. Rhoads and L. F. Craver. The white-cell count at that time was 17,300, and a little later 20,450. The patient was in the Memorial Hospital from October 22 until November 6. At first he received total body irradiation in two small doses, and a single dose of 200 r was subsequently applied to each of the six external lymph-node groups.

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‡Visiting physician, Hartford Hospital.

Unfortunately, however, a blood calcium determination was not made. We are unable to say whether or not the amino acid itself produced precipitation of the calcium salts, or even tubular necrosis.

The renal picture was interesting because of its clinicopathological correlation. The bladder was empty at post-mortem examination, despite ample fluid therapy. In spite of this anuria, however, the terminal blood urea nitrogen was 15 mg per 100 cc. With severe hepatic dysfunction producing a decrease in urea formation, this figure probably falsely implies normal renal function. In view of a urea nitrogen value of 11 mg three days previously and adequate parenteral fluids in the interim, it may have indicated early renal retention. A phosphorus determination in this particular case is more significant, for urea and creatinine figures probably mean little. Indeed, a significant rise of the serum phosphorus did occur concomitant with the development of anuria.

Urinary suppression was not present in Wilbur's¹³ cases of bile nephrosis. Nor was there clinical evidence of renal insufficiency in Ayer's¹⁰ infants with congenital biliary atresia. Although clinical renal failure was apparent in Ayer and Gauld's¹¹ cases of post-transfusion uremia, the morphologic alterations were essentially similar to those seen in the jaundiced infants. It was therefore considered unlikely that the morphologic changes in the kidneys after delayed reaction to transfusion were responsible for the renal failure observed clinically.

In the case presented above, however, the pattern of the kidney lesions seems significant. The calcium was present in considerable amounts in numerous tubules. The bile cylinders were situated proximal to the precipitated calcium. Furthermore, the tubular system proximal to the segments impregnated with calcium showed dilatation, whereas distally there was none. Histologically, therefore, there seems to have been evidence for an obstructive factor in the anuria in this case.

* * *

In their search for criteria for the safe administration of cinchophen, Palmer and Woodall⁷ were forced to admit the absolute unpredictability of its action. They found no method of administration that ensured against a fatal result. Previous ingestion, the absence of a history of allergy, the age and sex of the patient and even the dose seem to be of little value. In our case, for example, there was no history of allergy, the patient was a young child, and such as hepatic regenerates, and the absence of pre-existing disease is important, for it is well known that the liver has a considerable reserve from previous

FIGURE 4 Photomicrograph showing the dilatation of a distal convoluted tubule and mononuclear cells within the lumen.

rarely a bile cylinder. Bile casts, which were in the distal convolutions, were rarely associated with mononuclear cells within the lumen (Fig. 4). In distal convoluted tubules a dark-blue granular substance

liver disease, although it cannot exclude possible sensitization due to previous ingestion of cinchophen.

We have personal knowledge of at least 2 patients who developed urticaria following the ingestion of a single tablet of cinchophen. Short and Bauer,¹⁴ influenced by a study of 41 cases, considered this urticarial reaction an absolute contraindication to further cinchophen administration. Fink and Gay¹⁵ reported cases of urticarial rashes as long as three months after the discontinuation of atophan.

The usage of cinchophen is no longer widespread. If it must be employed, it should probably be reserved for the patient with severe gouty arthritis, especially in the interval between the acute attacks. Colchicine remains the drug of choice for the acute attack of gouty arthritis.

Our case of acute yellow atrophy beginning on the day after the ingestion of 2 gm of cinchophen terminated fatally twelve days later. The gross and histologic findings in the liver differed in some respects from those reported in cases of acute or fulminating hepatitis. Clinical and pathological evidence of pre-existing hepatic disease was absent. Urinary suppression and early phosphorus retention were featured. In addition to the usual picture of cholemic nephrosis, the kidneys showed considerable amounts of calcium within the collecting tubules and their peripheral branchings.

REFERENCES

1. Case records of the Massachusetts General Hospital (Case 11231). *Boston M & S J* 192 1122-1126, 1925.
2. Snyder, R. G., Traeger, C. H., Zoll, C. A., Kelly, L. C., and Lunt, F. J. Use of cinchophen in treatment of chronic arthritis. *J Lab & Clin Med* 21:541-547, 1936.
3. Reichle, H. S. Toxic cirrhosis of liver due to cinchophen. *Arch. Int. Med* 44:281-288, 1929.
4. Lucké, B. Pathology of fatal epidemic hepatitis. *Am J Path* 20:471-593, 1944.
5. Wood, D. A. Pathologic aspects of acute epidemic hepatitis, with special reference to early stages: report of series of ten cases, including case in which there was spontaneous rupture of spleen and six cases of fulminating disease in patients who had been wounded several months previously. *Arch. Path.* 41:345-375, 1946.
6. Lucké, B., and Mallory, T. Fulminant form of epidemic hepatitis. *Am J Path* 22:867-945, 1946.
7. Palmer, W. L., and Woodall, P. S. Cinchophen— is there safe method of administration? *J A M A* 107:760-764, 1936.
8. MacBryde, C. M. Toxic hepatitis and acute yellow atrophy following medication with cinchophen— containing "cold cure." *J A M A* 114:316-318, 1940.
9. Fahr, T. In Henke, F., and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*. Vol. 6, Part 1. Berlin: Julius Springer, 1925.
10. Ayer, D. Renal lesions associated with deep jaundice: with comments on their relations to those in so-called hepatorenal syndrome and in transfusion reactions. *Arch. Path.* 30:26-41, 1940.
11. Ayer, G. D., and Gauld, A. G. Uremia following blood transfusion: nature and significance of renal changes. *Arch. Path.* 33:513-532, 1942.
12. Flocks, R. H. "Early" calcium urolithiasis. *J A M A* 130:913-918, 1946.
13. Wilbur, D. L. Renal glomerulus in various forms of nephrosis. *Arch. Path.* 18:157-185, 1934.
14. Short, C. L., and Bauer, W. Cinchophen hypersensitivity: report of four cases and review. *Ann. Int. Med.* 6:1449-1464, 1933.
15. Fink, A. I., and Gay, L. N. Critical review of 170 cases of urticaria and angioneurotic edema followed for period of from two to ten years. *J. Allergy* 5:615-621, 1934.

Sections of the lymph nodes showed extensive destruction of the normal architecture by uniform infiltration of the dull appearing lymphocytes, typical of lymphatic leukemia.

Microscopical examination of the skin showed that the corium was extensively infiltrated by lymphocytes, a typical leukemic reaction. The remainder of the picture was consistent with lymphatic leukemia.

* * *

When this patient was seen at the Hartford Hospital in late January, 1943, he had a temperature of 103°F and was disoriented, the eyes were the only recognizable feature, and the end seemed imminent. Since there was a chance that female hormones

might be of value, other forms of treatment (Navitol and x-radiation) having been of no avail, Progynon was begun at once, and steady progress occurred until, in August, 1943, there remained only slight serous oozing about the ankles.

It may be argued that this case of leukemia cutis might have improved under some other treatment, or possibly with none. As a matter of fact, the symptoms diminished only with the use of hormones. If a similar case is seen, treatment with hormones certainly deserves serious consideration.

MEDICAL PROGRESS

EFFECTS OF PROTEIN DEFICIENCY ON THE PREGNANT WOMAN AND FETUS AND ON THE INFANT AND CHILD*

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BOSTON

MANY of the ill effects of a lack of sufficient or suitable proteins in the diet are encountered at all ages and in both pregnant and nonpregnant women. Some of them are particularly likely to occur during pregnancy, and others at certain periods of rapid growth in childhood when requirements are exceptionally high. The specific syndromes resulting from protein deficiency are not reviewed below, but attention is given to certain other effects that appear to be associated with pregnancy, with the health and development of the fetus, and with the progress of growth and development in infancy and childhood.

In the discussion of a single nutritional essential it must be kept in mind that except under conditions of rigid experimental control, attainable only in studies of animal nutrition, there are always many variables. For example, a diet low in protein is likely to be lacking in other essentials as well. Furthermore, the requirement for protein is modified by other characteristics of the diet. In some of the studies reviewed below the part played by protein is only implied, sometimes quite logically on the basis of all the known facts but at other times as a hypothesis to stimulate further study. For example, a woman who eats poorly and hence obtains too little protein may do so because of ignorance, disease or lack of money or because she is in a poor physical or psychologic state. Many other factors, therefore, must be considered, and supporting evidence is still required before one can conclude that protein per se is concerned with or primarily responsible

for certain complications of pregnancy or conditions of infants at birth that have been found to occur much more frequently when the maternal diet has been poorly provided with protein than when liberally provided. Also, a child who is constitutionally inferior may grow or develop in an unsatisfactory manner, not primarily because he eats a generally poor diet or one lacking in protein but because constitutional inferiority contributes both to poor appetite and to poor progress in growth and development. Again, it may be difficult to establish whether or not the poor physical state and progress are related to a poor nutritional background, and if so, whether inadequate protein is the principal dietary factor involved.

PROTEIN DURING PREGNANCY AND LACTATION

Increased Requirements

Several nitrogen-balance studies¹⁻⁴ have shown that women normally store relatively large amounts of protein during pregnancy. This positive nitrogen balance, according to Wilson⁵ and Macy and Hunscher,⁶ begins about the tenth or twelfth week of gestation and increases to term. Part of the protein is needed for the development of new maternal tissues, such as the breasts and uterus, and part is utilized in building the tissues of the fetus, including the placenta and membranes, but the total stored is in excess of these needs. The average fetal body at the sixth lunar month has been found to contain only 8 gm of nitrogen, whereas at term it contains 60 or 70 gm.^{1,2} The membranes and fluid at term contain about 19 gm, making a total for the mature ovum of 79 to 89 gm. An additional 17 gm of nitrogen is required on the average for the development of the mammary glands and 39 gm for the

*From the Department of Maternal and Child Health, Harvard School of Public Health. This review was prepared for and presented in part at "A Symposium on Body Protein" at the celebration of the one hundredth anniversary of the University of Buffalo, September 27, 1946.

†Professor of maternal and child health, Harvard Medical School, head, Department of Maternal and Child Health, Harvard School of Public Health, physician, Children's and Infants' Hospital.

On November 20 the patient weighed 166 pounds — this fact is mentioned because of the marked variations in weight, depending on the induration of the skin and the intensity of the edema. The skin over almost all the body was described as a "horrible brownish red." The patient was more animated and was working a part of each day. There were some large nodes in the groins, smaller ones in the axillae and still smaller ones about the jaw and the posterior chain in the neck. The spleen and liver were not palpable. The leonine expression of the face was striking, the color of the skin was a magenta red, and one of the most distressing symptoms was the constant itching, which made it impossible to refrain from scratching the face and head, especially the ears, which were greatly enlarged.

Examination of the blood at that time revealed a red-cell count of 4,310,000, with a hemoglobin of 13 gm (88 per cent), and a white-cell count of 20,600, with 9 per cent neutrophils (3 per cent myelocytes and other forms showing many toxic granules), 80 per cent lymphocytes (25 per cent large young forms and 55 per cent small forms) and 11 per cent smudges — probably lymphocytes. A subleukemic leukemia could not be excluded on this examination.

Navitol, which had been given daily in full doses of 150 drops, was discontinued, since it did not seem helpful and the patient thoroughly disliked it. The skin was much indurated, and the oozing from various areas required careful dressings each morning. No material change in the blood picture had occurred.

On January 30, 1943, the patient was seen in consultation by one of us (W H R) at the Hartford Hospital. He was disoriented. The temperature was 103°F. The skin, even on the scalp, was a dusky red, and much of the hair had dropped out, leaving only small scattered tufts, the nails had degenerated. There were oozing areas in which the itching was intense. The patient was so ill that he was given oxygen inhalations.

The use of female hormones was suggested, and treatment with Progynon B was immediately started in increasing doses, all forms of x-ray therapy were stopped.

There was marked edema, which raised the body weight to a maximum of 220 pounds and was relieved to a slight degree by a mercupurin suppository. On February 6 the edema had largely disappeared. The chest had become clear, and oxygen had not been given for 5 days. The weight had dropped from 220 to 190 pounds. The inguinal and axillary lymph nodes seemed to be somewhat larger and harder. The liver and spleen could not be felt. The loss of edema was remarkable. Navitol had been stopped for a week, but Progynon had been continued.

At that time the main problem was respiratory. Greater difficulty in breathing and rales over the entire chest persisted for several days before x-ray examination was performed. The lungs showed congestive changes and patchy areas of increased density, without evidence of lymph-node enlargement, that were interpreted as being due to infiltration of the lung tissue and to edema similar to that in the skin. X-ray treatment was considered valueless, and for several days oxygen was again administered. The skin and subcutaneous tissue had become definitely less edematous. The temperature was moderately elevated — 101 to 102°F. It was thought that Progynon might be credited with the weight loss. The patient seemed more comfortable, but although lucid at times, he was often confused and did not remember anything about the previous consultation.

On March 11 examination of the blood showed a hemoglobin of 81 per cent and a white-cell count of 28,100, with 31 per cent neutrophils, 65 per cent lymphocytes, 3 per cent eosinophils and 1 per cent monocytes. Ten per cent of the lymphocytes were young forms. The skin was continually desquamated and itchy. The circulation seemed adequate, and the urine was normal.

On March 25 diethylstilbestrol was added — in doses of 0.5 mg at first and subsequently 1 mg three times daily, the Progynon was administered as previously. Obundant ointment did more to relieve the itching than anything that had been tried. Early in May the whole condition showed improvement.

At the end of June the weight was 152 pounds, and the edema had practically disappeared except in the upper thighs, the scrotum was normal. The nails were growing, but the patchy baldness remained. There were some lymph nodes in the axillae and thighs. The liver was much smaller. The

skin over the entire body had become lighter in color. The breasts were slightly conical, and for that reason the dose of stilbestrol was reduced by half.

The hemoglobin was 11.7 gm (75 per cent), and the white-cell count 4200. A blood smear showed few white cells, the red cells approached normal in appearance. The platelets were small but numerous. In the stained specimen no abnormal cells were seen. The patient was anxious to be out and about, but since the thighs and legs were still large and heavy, walking was laborious.

On September 14, after making a motor trip of 120 miles, the patient arrived at his destination without undue fatigue, and his whole appearance was almost incredibly normal and healthy. The skin was clear and smooth, the hair had grown, and the appetite was excellent. Except for slight swelling about the ankles there was nothing unusual in his appearance.

In October the patient had recovered sufficiently to resume business on a half-day basis, he played eighteen holes of golf with ease, and his spirits were high. Stilbestrol had been discontinued for about 4 months, but Progynon had been taken, with a steady improvement in vigor and appearance. His condition was so satisfactory, even to complete freedom from desquamation in the legs and feet, that Progynon was stopped 3 months later.

On January 14, 1944, the patient developed a fine petechial rash over the chest and shoulders that was quite different from the original smooth erythema observed the year before. Although the hormones had not been given except in small doses for several weeks, the condition remained much improved, and the rash diminished after the Progynon was resumed in full doses. The blood picture was normal. A few young white cells were seen. On February 17 the patient saw Dr Craver, who considered the results in this case remarkable and who stated that resumption of Progynon was indicated in view of the reappearance of erythema in patches since its discontinuance.

On March 21 the condition was worse, the rash was confluent and the skin indurated.

In June, after a long course with Progynon, diethylstilbestrol and vitamins, the weight, which had risen in the preceding months, was reduced to 170 pounds, remaining at that level. There was little tendency to purpura, and the exudation was limited to the feet. The patient was considered definitely improved.

The rash seemed to be influenced by Progynon, for the petechial character became less marked and less brilliant. Since the rash seemed to the dermatologist and to the patient's own physician to be of quite a different character from that of the original, it was the desire of the dermatologist to discontinue the hormones for a time to see what effect purely local treatment would have. In July, however, the lymph nodes became larger, and the induration of the skin more marked. The edema and oozing increased. With all these changes the blood picture remained essentially the same. On September 6 another consultation took place while the patient was still at home. He was a dark red oozing mass, itching constantly and generally miserable. Three days later he was sent to the Hartford Hospital, where, on September 14, he died suddenly before the resident could reach his room. The manner of death suggested pulmonary embolus.

Autopsy. The anatomical diagnoses were chronic lymphatic leukemia, with leukemic infiltration of the spleen, liver, kidney and bone, leukemia cutis, thrombus in the right iliac vein, pulmonary embolus, with an infarct of the right lung, thrombus in the left renal vein and chronic cholecystitis with cholelithiasis.

The skin over the body showed a most remarkable appearance. Everywhere, from head to foot, it had a deep-red, scaly, thickened appearance. This was most prominent over the lower extremities, although it involved the upper chest, arms and face. On the lower extremities there were areas of ulceration between zones of thickened, scaly, red skin. These ulcerated areas, particularly those on the medial aspect, had a moist appearance. The skin on palpation had a brawny induration. The right leg was rather markedly edematous, and the left was atrophic in appearance. There was a moderate edema of the scrotum and penis. The skin was inelastic and thickened, and there was a diffuse edema of the subcutaneous fatty tissue, thin fluid exuded when the tissue was incised. The breasts appeared enlarged and when sectioned showed rather marked hypertrophy. The axillary lymph nodes were greatly enlarged, measuring up to 3 to 4 cm in diameter, they were of a soft consistence and had a pink appearance.

lactation About one and a half times the amount of protein secreted in the milk is needed in the diet to provide for this—that is, about 25 to 30 gm per liter of breast milk. The National Research Council's⁹ recommended allowance for the lactation period is 100 gm of protein daily—40 gm above that of the nonpregnant, nonlactating woman. This allowance seems to be liberal and sufficient to allow for individual differences in requirement and utilization. Various reports from famine areas indicate that when women are markedly underfed, they are unlikely to produce an adequate supply of breast milk. Protein deficiency appears to be an important factor, although probably not the only one involved in these situations. Garry and Wood¹⁶ have suggested that the negative nitrogen balance frequently encountered in lactation may be conditioned by an energy intake too low for all the demands made on the lactating woman. Since the caloric requirement is markedly increased during lactation, it is clear that calories as well as protein must be considered. The successful nursing mother has been shown by Kaucher¹⁷ to select usually a high-protein, high-calorie diet. Emotional instability is likely to affect the appetite adversely and is detrimental to successful nursing.

On the basis of these considerations, it seems to be important that a woman end pregnancy with liberal stores of nitrogen, and that she consume in the neighborhood of 2 gm of protein per kilogram of body weight, or about 100 gm a day, during lactation.

Effects of Maternal Protein Deficiency

Conception rate Before the effects of low protein intake and generally deficient diet on the pregnant woman and the fetus are considered, it should be pointed out that severe dietary deficiency leads to amenorrhea and inability to conceive. This is a well established result of gross underfeeding in animals and one that must be considered in all animal experimentation. It has been found to have occurred in a number of areas where human starvation was in progress. According to Smith,¹⁸ whose interesting observations are further considered below, the conception rate in Holland during the hunger winter of 1944–1945 fell to 30 per cent of normal. How much of this was due to absence of husbands and how much to malnutrition cannot be determined, but the latter was clearly a major factor. Sixty per cent of the women of menstrual age in the large cities of Holland developed amenorrhea, and there was a correspondingly sharp fall in the birth rate. Antonov¹⁹ also reported a marked fall in the birth rate in Leningrad during the siege. Sydenham²⁰ recently reported the occurrence of amenorrhea among British civilian internees in the Stanley Camp at Hong Kong, China. During the months in which the diet was low in protein but adequate in calories, many women remained amenorrheic

without losing weight. The incidence of amenorrhea fell sharply after supplies of tinned meat became available through Red Cross shipments. Sydenham concluded that although emotional shock or change of environment may have explained many of the irregularities of menstruation and the early cases of amenorrhea of short duration, the 53.7 per cent of patients with amenorrhea lasting more than three months—in some cases lasting a year or more—could hardly be explained on this basis. Malnutrition, especially deficiency of protein, appeared to be the most probable cause.

Complications of pregnancy Williams¹⁰ has recently reviewed the relation between protein nutrition and the course of pregnancy. He refers to the customary evidence of protein deficiency, such as depletion of body tissues, lowered serum protein, nutritional edema and lowered resistance to infections. Although these manifestations of protein deficiency occur more frequently under the stress of pregnancy, they are not peculiar to this state and are therefore not considered here. Williams considered at greater length the possible relations between protein nutrition and toxemia, the anemias of pregnancy, poor uterine muscle tone and lowered resistance to special infections during the puerperium. These may be regarded as the more particular problems of protein malnutrition affecting the health of the woman during pregnancy.

Since the cause of toxemia of pregnancy is still obscure, one who is not an obstetrician hesitates to discuss this complicated subject. Recent studies of Smith and Smith²¹ point to a true toxin resulting from damage to the uterine tissue associated with abnormal estrin-progestin metabolism. Nevertheless, it may be accepted that the ultimate cause of this complication of pregnancy remains to be established, and it seems clear from several recent studies that protein metabolism is a factor of possible significance. Unquestionably, many influences are concerned, but this review restricts attention to the evidence regarding the relation of dietary protein to the incidence of toxemia.

A number of workers^{11, 22–27} have presented evidence that the incidence of toxemia is far higher among women whose intakes of protein are markedly deficient or whose diets are generally poor than among those whose diets are generally good or are well supplied with protein. The difficulties involved in human studies in proving whether or not a given nutrient is responsible for a given effect are apparent to those who have attempted to investigate these relations further. Strauss²² has contended that the most plausible assumption is that in the presence of protein insufficiency the colloid osmotic pressure of the serum protein is altered. This causes edema and a consequent disturbance in the electrolyte balance that, in turn, results in elevation of the blood pressure and other symptoms of toxemia. In such circumstances, protein may serve as a protec-

uterus,⁵ making 56 gm the amount needed on the average for the growth of maternal tissues. On the basis of these findings, it has been estimated that about 135 to 145 gm of nitrogen beyond maintenance needs is required during pregnancy, or about 845 to 900 gm of protein.⁷ Macy and Hunscher⁶ and Wilson⁵ have shown that under favorable circumstances the amount of nitrogen actually stored is 200 to 400 gm, representing 1250 to 2500 gm of protein, in excess of the probable utilization by the mother for herself and for the fetus in the replacement of old tissues or the construction of new.

A negative nitrogen balance sets in abruptly just before term,⁶ and there is a substantial loss of nitrogen from the maternal organism during parturition and the post-partum period. For women who nurse their infants, there is an additional loss in the breast milk amounting to about 1 to 1.5 gm of nitrogen a day, depending on the amount of milk secreted. Thus, it is usual to find a negative nitrogen balance throughout the puerperium, and often during the lactation period as well. The reserve of nitrogen stored during pregnancy, therefore, may be regarded as in part a natural mechanism to provide in advance for the large losses occurring during delivery and the puerperium, and in part for the high requirements of lactation.

The actual increase in dietary protein required to meet the needs of pregnancy is a matter of debate. From the calculations regarding nitrogen requirements discussed above and from studies by Burke et al.⁸ of the condition of the infant at birth in relation to the level of maternal dietary protein, an increase in the protein of the diet during the last six months of pregnancy of 15 to 20 gm a day above the woman's normal requirements may be assumed to be the average need.

If it is assumed that an allowance of 60 gm of protein is desirable and adequate for the average nonpregnant woman and that an increase of 15 to 20 gm daily is needed for these special purposes in pregnancy, the allowance recommended by the Food and Nutrition Board of the National Research Council⁹ of 85 gm during the latter part of pregnancy seems to be liberal and sufficient to take care of individual differences. Williams,¹⁰ in a review of this subject, emphasized the important point that this figure presupposes a previously normal protein intake and nutritional state.

The question immediately arises of how nearly the diets of pregnant women approximate this allowance. Burke,⁸ in studies at the Boston Lying-in Hospital, found that the diets in 68 per cent of 216 pregnant women contained less than 70 gm, those in 38 per cent, less than 55 gm and those in 14 per cent, less than 45 gm of protein daily. Arnell¹¹ in studies of 400 pregnant women in New Orleans found that 18 per cent took less than 42.5 gm of protein daily—that is, less than half the allowance recommended by the National Research

Council—and 79 per cent less than 70 gm. In dietary studies on 514 pregnant women in Philadelphia, Williams¹² found that only 13 per cent were taking 85 gm of protein daily as recommended. Since many women habitually take a poorly balanced diet that is low in protein and do not change their habits appreciably during pregnancy, it is not surprising that the usual signs of protein malnutrition are encountered more frequently when the physiologic strain of pregnancy is superimposed on normal requirements.

The need for protein in the mother's diet during lactation has received considerable attention. In the dairy industry the value of a liberal intake of protein during the latter part of gestation for successful milk production has long been recognized.¹³ In women, psychologic factors have such an important influence on milk production that the relation of diet and nutrition to milk supply is difficult to demonstrate. The evidence suggests that diet during pregnancy—and possibly before—has at least as much to do with a satisfactory supply of breast milk as the diet during lactation. Macy and her associates¹⁴ have shown that a high-protein diet during the latter part of pregnancy is important for successful nursing, and that a diet high in animal protein results not only in the highest nitrogen retention but also in the highest milk yield.

Orr and Gilks¹⁵ studied lactation and growth in a South African tribe that lived principally on cereals, roots and legumes and lacked milk and other suitable infant foods. The mothers in this tribe were unable to nurse their babies successfully for an average of more than three months, and after three months the infants grew poorly. In contrast, the mothers of a pastoral South African tribe, living mainly on animal foods, continued to nurse their babies successfully for long periods. The differences in size and physique of the infants of these two tribes became progressively more striking from three months onward.

Without going farther into the details of the controversial literature on the relation of diet and nutritional status to lactation, the following tentative generalizations seem to be justified. Women differ considerably in their capacity to develop breast tissue, and the development of the breasts during pregnancy may be further restricted by chronic malnutrition or by a lack of adequate protein. The quantity of milk that any woman secretes is determined only in part by breast development, for it is influenced by mechanical, psychologic and nutritional factors. Under favorable conditions a woman secretes milk at the expense first of the dietary protein and then of the protein tissues. She continues to do so for long periods, with a resultant negative nitrogen balance. How long or successfully she will secrete an adequate supply depends in part on the protein intake and nitrogen storage during pregnancy, as well as on the protein intake during

They believe that it is probably dependent on a lack of complete proteins but possibly also on a deficiency of one or more of the factors in the vitamin B complex. This type of anemia usually responds to an increased intake of animal protein and of the factors of the vitamin B complex.

Labor and delivery. There is little evidence that protein deficiency in the mother contributes directly to prolonged or difficult labor and to other complications at or following delivery. Poor development of the uterus was found by Wallace³¹ to be a striking end result of low protein low-calorie diets in sheep. Uterine inertia and prolonged labor have often been considered attributable in individual cases to poor nutritional state. In the studies at the Boston Lying-in Hospital the average length of labor of the primiparous women was the same in the group with poor diets as in that with good diets.²² It is of interest, however, that in this series of 216 cases there were many more difficult types of delivery in the patients with poor to very poor diets than in those with good or excellent ones, despite the fact that the infants in the former group were on the average 3 pounds lighter in weight. It is generally recognized that large babies make for more difficult deliveries than small ones do. Hence, other things being equal, the mothers with poor diets should have had shorter labors and easier deliveries. The assumption may therefore be made that the women in the poor-diet group were not otherwise so fit for labor.

Frequency of abortions and stillbirths. Arnell,¹¹ in the studies referred to above, showed that when the maternal dietary protein was 85 gm or more there was no fetal mortality and that when it was between 70 and 85 gm daily the mortality was only 2.2 per cent. On the other hand, when the protein consumed was between 42.5 and 54 gm, the fetal mortality rose to 5.5 per cent. In another report of the 216 cases referred to above,²² there were no abortions probably because enrollment was not until the end of the third month or later. There were, however, 5 stillbirths, all of which occurred in pregnancies of women with very poor diets. All the women whose babies were stillborn consumed diets that were inadequate in protein, and in all but 1 case the calories were rated inadequate. Two of the 3 neonatal deaths in this series also occurred in the group with poor to very poor maternal diets. Ebbs⁴ found that of the 14 infants lost in a total of 310 pregnancies, all were in the group with poor maternal diets. There were 7 miscarriages, 4 stillbirths and 3 neonatal deaths in his series. Williams,¹² however, found no relation between maternal diet and the condition of the infant at birth.

Smith's¹⁸ data from Holland are inconclusive on these points as are the figures of Antonov,¹⁹ which cover the period of the siege in Leningrad. It is impossible to draw conclusions from changes in rates representing proportions of live births, when

the birth rates were changing as rapidly as they were in Holland and Leningrad at the times of these studies.

Premature births. In our studies in Boston all prematurely born babies — that is, infants weighing less than 2.25 kg (5 pounds) at birth — were born to mothers whose diets were in the lowest general rating. Here again, the work of Ebbs,²⁴ the Peoples League of Health²⁵ and Balfour,²⁶ showed the same trend, but that of Williams¹² failed to do so. Smith¹⁸ also found a slight but not statistically significant increase in the percentage of births of infants weighing under 2.25 kg during the hunger period in Holland. Antonov¹⁹ observed that the rate in Leningrad was 41.2 per cent of the total births during the siege but fell to 6.5 per cent in the first

TABLE 1. *Relation of Birth Weight and Length to Total Protein in Maternal Diet during Last Six Months of Pregnancy (according to Barke et al²⁷)*

AVERAGE TOTAL PROTEIN ^a	BIRTH WEIGHT*		BIRTH LENGTH	
	MALE INFANTS	FEMALE INFANTS	MALE INFANTS	FEMALE INFANTS
	lb	oz	cm	cm
Less than 45	6	8	47	46
45-54	7	0	49	48
55-64	7	7	50	49
65-74	8	0	51	50
75-84	8	5	52	51
85 and over	9	2	53	52

*No infants weighing under 5 pounds included.

six months after it had ended. The marked reduction in the birth rates during these periods complicates the interpretation of these figures as they do those for abortions and stillbirths.

The evidence suggests that inadequate protein during pregnancy, especially when enhanced by inadequate calories, increases the chances of premature onset of labor. Again, it must be concluded that although poor maternal diets and a high incidence of abortions, stillbirths, premature births and neonatal deaths are frequently associated, the nature of this relation is not yet known.

Size and development of the infant at birth. The evidence regarding the association between maternal diet and the size and development of the infant at birth is much stronger and more convincing than that for the relations thus far considered. It is difficult to separate exactly the infants who are small and poorly developed at birth because of premature onset of labor and those who have reached full term showing evidences of retarded fetal growth and development. The former is primarily a maternal effect, and the latter a fetal one. For this purpose premature birth is usually determined arbitrarily on the basis of a selected birth weight, and in our studies a weight of 5 pounds has been used. Table 1 presents birth weights and birth lengths according to the quantity of protein in the maternal diet during pregnancy.

tive or therapeutic agent by virtue of its chemical and physiologic properties, rather than as a source of building materials for new tissues, as in most of the situations being considered

Studies of pregnancies in 216 cases have been reported by Burke and her associates²⁷ at the Harvard School of Public Health. The patients were followed at the Boston Lying-in Hospital, with detailed dietary histories each trimester, and the diets were graded into five categories from "very poor" to "excellent." There were 28 cases of toxemia in the series. The incidence of this condition was 44 per cent among the patients whose general diets were rated "poor" to "very poor" and 8 per cent among those rated "fair," whereas among those rated "good" or "excellent" not a single case developed. This association between generally poor diet and high incidence of toxemia is impressive and has statistical significance, but when analyzed on the basis of protein alone the relation was not statistically important, although in the same direction. The number of cases is too few to justify conclusions, and further study is required. Arnell¹¹ found a higher incidence of toxemia among patients with a low-protein diet than among those with a liberal protein diet. Holmes²² reported that the incidence in groups of 350 primiparous and 350 multiparous women taking low-protein diets was twice as great as that in similar groups taking high-protein diets. On the other hand, Dieckmann²⁸ could not confirm this relation and has expressed the view that toxemia and a low-protein intake are not related.

Reports from certain areas in which true starvation occurred during World War II, as well as during World War I have indicated that the incidence of toxemia fell sharply among pregnant women during the periods of extreme food restriction. In studies of pregnancies and their outcome at the midwifery school of Rotterdam, Holland, before, during and following the acute famine of 1945, Smith¹⁸ obtained rather surprising figures regarding the incidence of toxemia. During the months of acute hunger the incidence fell to about half that occurring in the same institution during the pre-hunger and post-hunger periods. The diets of pregnant women from January to April, 1945, of the so-called "hunger winter" provided according to the ration figures approximately 750 to 900 calories and 35 to 40 gm of protein. Although there is no way of knowing how much additional food these women may have had, it is safe to assume that even at best the diets during this period were low in both calories and protein, as well as in minerals and vitamins.

The studies of the results of war shortages on toxemia are in such sharp contrast to those of other maternal dietary studies that one must examine the data carefully for an explanation of the differences. In Holland the hunger period was one of brief duration, rarely affecting more than half of any pregnancy, and the pre-hunger period provided rela-

tively good nutritional circumstances. The more detailed dietary studies in the United States, in contrast, indicate that the women with poor diets for the most part had habitually consumed such diets before and during pregnancy. In Holland the hunger diet was one of low calories and roughly parallel reduction in protein and other essential nutrients, whereas in this country the poor diets were usually poorly balanced providing more or less adequate, sometimes excessive, calories drawn largely from classes of foods that carried little protein and other structural and regulatory essentials. A factor that may have influenced the results in Holland was the sharp fall in the conception rate. It could well be that the women in Holland who were chronically undernourished, and hence presumably predisposed to the development of toxemia, became amenorrheic in a relatively short time on such an inadequate diet and hence did not conceive. The potentially toxemic women may thus have been removed temporarily from the population of the maternity hospital.

Although there is still controversy among well informed persons concerning the cause of toxemia, it is generally accepted that a high-protein diet does not predispose the patient to the condition. Furthermore, the major weight of evidence appears to be that toxemia occurs oftener among chronically malnourished than among well nourished women, protein being one of the nutritional factors frequently lacking. Most workers, including those in my group and others who have obtained similar results, are agreed that although definite conclusions cannot yet be drawn the subject is an important one for further investigations.

Anemias of pregnancy. A physiologic reduction in the number of red cells and in the hemoglobin takes place normally in midpregnancy and is apparently a dilution phenomenon. The hypochromic anemia often seen in late pregnancy is generally considered to be an exaggeration or prolongation of this physiologic change. Bethell,²⁹ reporting a 25.4 per cent incidence of anemia in a group of 484 pregnant women in Michigan, found a relation between deficiency of dietary iron and hypochromic anemia. This type of anemia often responds poorly to iron therapy alone and has been reported to respond much more satisfactorily to a combination of a diet high in animal protein and medicinal iron.

True macrocytic anemia of pregnancy is rarely encountered in this country. Bethell, in the study mentioned above, found a relation between macrocytic anemia and an inadequate intake of protein. Severe macrocytic anemia of pregnancy is reported to be frequent in India. This type of anemia carries with it high maternal and high fetal mortality rates. Napier and Neal-Edwards,³⁰ who have studied the condition extensively in India, point out that its incidence is highly correlated with a low economic status and with diets low in protein of animal origin.

22. Strauss, M. B. Observations on etiology of toxemias of pregnancy IV Primary role of plasma proteins in conditioning water retention and edema formation in normal and "toxemic" pregnancy. *Am. J. M. Sc.* 195 723-728 1938
23. Holmes, O. M. Protein diet in pregnancy. *West J. Surg.* 49 56-60, 1941
24. Ebbs, J. H., Tisdall, F. F., and Scott, W. A. Influence of prenatal diet on mother and child. *J. Nutrition* 22 515-526, 1941
25. Interim Report of People's League of Health. Nutrition of expectant and nursing mothers. *Lancet* 2 10-12, 1942
26. Balfour, M. I. Supplementary feeding in pregnancy. *Lancet* 1 208-211, 1944
27. Burke, B. S., Beal, V. A., Kirkwood, S. B., and Stuart, H. C. Nutrition studies during pregnancy. I. Problem, methods of study and group studied. II. Relation of prenatal nutrition to condition of infant at birth and during first two weeks of life. III. Relation of prenatal nutrition to pregnancy, labor, delivery and postpartum period. *Am. J. Obst. & Gynec.* 46 38-52, 1943
28. Dieckmann, W. J. Edema in pre eclampsia and eclampsia. *Ar. J. Obst. & Gynec.* 41 1 16 1941
29. Bethell, F. H., Blecha, E., and Van Sant, J. H. Nutritional inadequacies in pregnancy correlated with incidence of anemia. *J. Am. Diet. A.* 19 165-172, 1943
30. Napier, L. E. and Neal-Edwards, M. I. Anaemia in pregnancy in Calcutta. Analysis of haematological and other data from 529 pregnant women. *Indian M. Research Mem.* No 33 pp 1-135 1941
31. Wallace, L. R. Unpublished thesis (Department of Agriculture Cambridge University)
32. Burke, B. S., Beal, V. A., Kirkwood, S. B. and Stuart, H. C. Influence of nutrition during pregnancy upon condition of infant at birth. *J. Nutrition* 26 569-587 1943
33. Smith, C. A. Effects of maternal undernutrition in Holland (1944-45) upon newborn infant. *J. Pediat.* (in press)
34. Stuart, H. C. Findings on examinations of newborn infants and infants during neo-natal period which appear to have relationship to diets of their mothers during pregnancy. *Federation Proc.* 4 271-281 1945

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 33141

PRESENTATION OF CASE

First admission. A nineteen-year-old unmarried girl was admitted to the hospital because of pain in the lower back.

For three years the patient had suffered from pain over the coccygeal region. The pain was nonradiating and was aggravated by long sitting or standing, but was not noticeably increased by rising or sitting down. She had noticed some tenderness and pressure over that area. A year prior to admission a pilonidal sinus had been removed from the area, without relief from pain. She suffered a great deal from riding in an automobile and sitting in a soft seat, and the pain was often worse at night.

No contributory past history was obtained.

On physical examination the only positive finding was pain on pressure over the coccygeal region and just to the right of the scar from the operation for pilonidal sinus. Examinations of the blood and urine were negative, except for a white-cell count of 12,700. The differential count was normal. A blood Hinton test was negative. X-ray films taken in the Out Patient Department before admission revealed the coccyx to be poorly visualized and somewhat fragmented. There was a faint suggestion of a soft-tissue mass, measuring 5 cm., in the midline, at the extreme distal tip of the coccyx.

X-ray examination on admission revealed that the lower segments of the coccyx were absent. The previous films were not available for comparison.

While in the hospital the patient noted a small amount of mucus in the stool and stated that she had noticed this once or twice about two or three months previously. She denied any pain during bowel movements. There had never been any blood in the stools, although the mucus had once been slightly pink. After sigmoidoscopic examination the pain disappeared completely, and the patient was surprised at her ability to lie in any position. Three days later the pain was still only mild. A psychiatrist discovered considerable emotional problems relating to the family. He thought that the patient was somewhat emotionally immature. The mother was domineering, and there was competition with a brother for parental affection. Study on the psychiatric service was recommended. The patient was discharged with instructions in gluteal exercises and sitting.

Final admission (five months later). The patient was followed in the Psychiatric Out Patient Clinic without improvement. Five months later she was noted to have erythema and induration in the region of the scar, possibly as a result of excessive physical therapy. She was noted to be stooping somewhat and was again admitted to the hospital. She localized the pain largely to the tip of the sacrum. No mass was felt by several examiners. Examinations of the blood and urine were negative. An x-ray film revealed that the coccyx and lower segment of the sacrum were missing and there was a soft-tissue mass, measuring 7 by 4 cm., within which there were areas of calcification or bone remnants. The edge of the remaining segment was somewhat ragged. Subsequent to this report an extremely hard, tender mass was palpable by rectum or pelvic examination corresponding to the x-ray finding at the lower end of the sacrum. An x-ray film of the chest was negative. The blood calcium was 8.9 mg., and the phosphorus 3.3 mg. per 100 cc., and the phosphatase 15.7 Bodansky units.

About a month after admission an operation was performed.

The progressive increase in average birth length and birth weight with increasing amounts of dietary protein during the latter part of pregnancy is striking

Smith,³³ in his study of birth weights and birth lengths in Holland, found a sharp drop during the hunger winter and an almost equally abrupt rise as Holland emerged from the period of severe malnutrition. This association between the size of the newborn and the adequacy of rations may well have depended on the protein content of the maternal diet as well as on the caloric content, since the Dutch diets were known to be low in protein during this period and since low calories make the diet even less satisfactory in protein. In studies of babies born in Leningrad during the siege, Antonov¹⁹ showed similar trends in birth weights, the average during the first half of 1942 being approximately 0.5 kg. lower than that for the corresponding period of 1941 before the siege. During the second half of 1942 (after the siege), the average weight had risen about half the amount lost.

Wallace³¹ has shown that when the diets of sheep are made low in calories and protein in the last half of pregnancy the weight and length of the newborn are markedly lowered. Using the same mother animal Wallace reversed the results by increasing these components of the dietary intake of the pregnant animal. Whereas it is not possible to say from these experiments that protein was the only factor responsible for the differences in the rates of growth of the fetuses, it is possible to conclude that the combined intake of calories and protein in the latter part of pregnancy was the primary variable.

The relations found by my associates in Boston, the evidence of Smith from Holland, the work of Antonov in Leningrad and recent English studies reviewed by Garry and Wood¹⁶ provide strong evidence that if the diet is low in protein during the latter part of pregnancy, there is a tendency for the infant to be born prematurely or to be relatively immature at birth.

Evidence of retarded osseous development in infants born to mothers whose diets were poorly provided with protein has been presented.³⁴ Osseous ratings of "advanced," "average" and "retarded" were given on the basis of the presence or absence of certain osseous centers at birth in roentgenograms of the knee, hand and foot. When the maternal diet was excellent in protein, 57 per cent of infants were advanced in osseous development, and 14 per cent retarded, whereas when the maternal diet was very poor in protein no infants were advanced and 71 per cent were retarded. Although this relation appears to be significant, it must be remembered that certain other nutrients closely associated with protein in food may have been involved. It is known, however, that protein forms the matrix for bone growth, and there are other reasons for

believing that protein may be the principal factor. Wallace³¹ has presented data on sheep that tend to confirm this relation. He found much poorer skeletal formation in the young of the sheep inadequately fed in protein and calories in the latter part of pregnancy than in those well fed during this period.

The studies of Wallace referred to above showed that changes occurred in the maternal stores of protein in conjunction with changes in the diets. His results indicate that the fetus is parasitic on the mother only to a degree and that when her protein stores are depleted to any major degree she appears to retain the remaining stores as if some protective mechanism were operative. These studies also show that when the maternal animals are starved in relation to calories and protein in the latter part of pregnancy the livers of the young are small, the increase in size during the last half of pregnancy being approximately 8 per cent of normal.

(To be concluded)

REFERENCES

- Hunscher, H. A., Donelson, E., Nims, B., Kenyon, F., and Macy, I. G. Metabolism of women during reproductive cycle. V Nitrogen utilization. *J. Biol. Chem.*, 99:507-520, 1933.
- Coons, C. M., Schiefelbusch, A. T., Marshall, G. B., and Coons, R. R. Studies in metabolism during pregnancy. *Oklahoma A & M College Agric. Exper. Stat. Bull.* 223:1-113, 1935.
- Adair, F. L., Dieckmann, W. J., Michel, H., Dunkle, F., Kramer, S., and Lorange, E. Calcium, phosphorus, iron and nitrogen balances in pregnant women. *Am. J. Obst. & Gynec.* 46:116-121, 1943.
- Oberst, F. W., and Plass, E. D. Calcium, phosphorus and nitrogen metabolism in women during second half of pregnancy and in early lactation. *Am. J. Obst. & Gynec.* 40:399-413, 1940.
- Wilson, K. M. Nitrogen metabolism during pregnancy. *Bull. Johns Hopkins Hosp.* 27:121-129, 1916.
- Macy, I. G., and Hunscher, H. A. Evaluation of maternal nitrogen and mineral needs during embryonic and infant development. *Am. J. Obst. & Gynec.* 27:878-888, 1934.
- Garry, R. C., and Stiven, D. Review of recent work on dietary requirements in pregnancy and lactation, with attempt to assess human requirements. *Nutrition Abstr. & Rev.* 8:855-887, 1936.
- Burke, B. S., Harding, V. V., and Stuart, H. C. Nutrition studies during pregnancy. IV. Relation of protein content of mother's diet during pregnancy to birth length, birth weight and condition of infant at birth. *J. Pediatr.* 23:506-515, 1943.
- Food and Nutrition Board, National Research Council. *Recommended Dietary Allowances* (Reprint and Circular Series, No. 122, pp. 1-18, 1945).
- Williams, P. F. Importance of adequate protein nutrition in pregnancy. *J. A. M. A.* 127:1052-1055, 1945.
- Arnell, R. E., Goldman, D. W., and Bertucci, F. J. Protein deficiencies in pregnancy. *J. A. M. A.* 127:1101-1107, 1945.
- Williams, P. F., and Fralin, F. G. Nutrition study in pregnancy: dietary analysis of seven-day food intake records of 514 pregnant women, comparison of actual food intakes with variously stated requirements and relationship of food intake to various obstetric factors. *Am. J. Obst. & Gynec.* 43:1-20, 1942.
- Meigs, E. B. Milk secretion as related to diet. *[Physiol. Rev.]* 2:204-237, 1922.
- Shukers, C. F., Macy, I. G., Nims, B., Donelson, E., and Hunscher, H. A. Quantitative study of dietary of human mother with respect to nutrients secreted into breast milk. *J. Nutrition* 5:127-139, 1932.
- Orr, J. B., and Gilks, J. L. *Studies of Nutrition. The physique and health of two African tribes*. 82 pp. Medical Research Council Special Reports Series No. 155. London: His Majesty's Stationery Office, 1931.
- Garry, R. C., and Wood, H. O. Dietary requirements in human pregnancy and lactation. Review of recent work. *Nutrition Abstr. & Rev.* 15:591-621, 1946.
- Kaucher, M., Moyer, E. Z., Williams, H. H., and Macy, I. G. Adequacy of diet during lactation. *J. Am. Diet. A.* 22:594-601, 1946.
- Smith, C. A. Effects of war time starvation in Holland upon pregnancy and its products. *Am. J. Obst. & Gynec.* (in press).
- Antonov, A. N. Children born during siege of Leningrad in 1942. (Based on records of Department of Newborn Children of Leningrad State Pediatric Institute.) Unpublished report.
- Sydenham, A. Amnorrhoia at Stanley Camp, Hong Kong, during internment. *Br. M. J.* 2:159, 1946.
- Smith, G. V. S., and Smith, O. W. Cited by Kellogg, F. S. Toxemia of pregnancy. *Chinica* 4:585-647, 1945.

the patient has had no subsequent difficulty. Although this is a rare location for a benign giant-cell tumor, it is a possible one.

Dr. Simmons, have you anything further to say?

Dr. SIMMONS: In any of these cases in which the radiologists and clinicians are at a loss regarding the diagnosis, when the pathologist gets the section he may be puzzled too.

CASE 33142

PRESENTATION OF CASE

A forty-seven-year-old housewife entered the hospital because of a mass in the right axilla.

Three years before admission pain and weakness had developed in the right shoulder and axilla. A mass was discovered. The pain disappeared after a course of x-ray treatment. A year and a half later a second course of x-ray therapy was given because of the reappearance of pain. A few weeks before admission the mass was again present and somewhat painful. Three and two weeks prior to admission single doses of x-ray therapy were directed at the axilla. There was doubt whether irradiation altered the size of the mass.

No masses had ever been felt in the breasts, nor had there been pains in other parts of the body. No lymph-node enlargement had ever been noted. The system review and past history were noncontributory.

Physical examination showed a large, obese woman who weighed about 220 pounds and appeared in good health. In the right axilla there was a mass measuring 8 by 8 cm. that moved with the scapula. It felt firm but not stony hard, and was smooth and slightly tender. The overlying skin was not adherent, nor was the mass adherent to the chest wall. No lymphadenopathy was present.

The temperature, pulse and respirations were normal. The blood pressure was 190 systolic, 110 diastolic.

Examination of the blood revealed a hemoglobin of 13.6 gm per 100 cc and a white-cell count of 6200, with 53 per cent neutrophils. The urine gave a + test for albumin, and the sediment contained 25 red cells and 15 white cells per high-power field. The blood calcium was 8.9 mg, the phosphorus 2.2 mg, and the total protein 7.3 gm per 100 cc, and the phosphatase 3.0 Bodansky units. On x-ray examination the heart and lungs appeared normal. There was evidence of an old healed fracture of the distal third of the right clavicle. There was an oval soft-tissue mass in the medial wall of the right axilla, measuring approximately 11 by 6 cm. The outer wall was fairly well demarcated and smooth in outline. The upper two thirds of the lateral border of the scapula was irregular in outline.

An operation was performed on the eighth day.

DIFFERENTIAL DIAGNOSIS

Dr. GRANTLEY W. TAYLOR: The history is deplorably silent about whether the tumor disappeared after x-ray treatment. Perhaps we should see the x-ray films.

Dr. TOUFIC H. KALIL: The soft-tissue mass is best seen on this film. It measures 11 by 6 cm. and has a smooth, well defined outer border. The involved portion of the scapula is demonstrated by the irregular lateral margin produced by a small amount of bone destruction.

Dr. TAYLOR: In a discussion of the diagnosis of these lesions involving bone in the preceding case Dr. Simmons referred to the possibility of confusing inflammatory conditions and metabolic disturbances with bone tumors. It seems to me that we have nothing to suggest an inflammatory process or any generalized metabolic disturbance in this case. We are dealing with an axillary tumor, and there is little to go on except the tumor itself, the x-ray findings and the fact that the patient was apparently well in spite of the presence of tumor for over three years.

Was this a tumor of bone with soft-part extension, or tumor of the soft parts with erosion or irregularity of bone because of the propinquity of the process to the bone? I do not believe that one can say definitely. Dr. Kalil might like to make a statement regarding whether that amount of bone distortion could be due to impingement of a tumor on the soft parts.

Dr. KALIL: I should expect a smooth erosion rather than this type of irregularity in such a case.

Dr. TAYLOR: When we consider the bone tumors in this region we at once raise the question whether they are benign or malignant. In favor of a benign tumor in the case under discussion is the long course and the patient's excellent health in spite of the long course. We have one additional fact in the history that may be of some significance — namely, that x-ray treatments had been used, with adequate control of the symptomatology for some time. It would be helpful to know whether there was any change in the mass as a result of the previous irradiation. It is interesting that x-ray therapy relieves the pain in many conditions, in which it can almost be regarded as a type of physiotherapy. There seems to be something specific about the relief of pain by x-ray treatment in a large diversity of cases that are not necessarily neoplastic or malignant.

Dr. Kalil is unwilling to say that this amount of bone disease was due to the pressure of an adjacent tumor of the soft tissue. We must concentrate on bone tumors or tumors that may involve bone. Of the malignant tumors we must consider whether we are dealing with metastatic or primary tumors. This was a perfectly healthy person with nothing in the history to suggest metastases from any other part of the body. The one positive finding on laboratory examination was that the urinary sediment con-

DIFFERENTIAL DIAGNOSIS

DR CHANNING C SIMMONS In all these cases of bone lesions three main conditions should be borne in mind skeletal disease, an inflammatory condition and tumor, either primary or metastatic. Keeping these possibilities in mind, let us analyze this case. The patient was highly nervous, and complained of pain in the region of the coccyx. She had been operated on five months previously for pilonidal sinus. The pain was relieved by sigmoidoscopy. The x-ray films showed some trouble with the coccyx. Reading between the lines I believe that, at that time, a diagnosis was probably made of a low-grade infection, such as osteomyelitis, secondary to the pilonidal sinus. Why the pain was relieved by sigmoidoscopy, I do not know, that is not the ordinary treatment for either osteomyelitis or coccygalgia. I also do not know why nothing more was done after the findings showed a definite lesion of the coccyx.

May we see the first x-ray films?

DR TOUFIC H KALIL This is the soft-tissue mass referred to, and in the lateral view it can be seen extending down to replace the coccyx. The ragged appearance of the bone denotes destruction.

DR SIMMONS The patient was readmitted with a definite mass in that situation, and the pain continued. In this second series of films the mass appears larger than it was previously.

The one positive finding other than tumor is the high phosphatase in the blood. From the description of the x-ray examination there was bone destruction with new bone formation in the tumor, and the high phosphatase was probably due to new bone formation. We can rule out disease of the liver and kidney, in which the phosphatase may be high. The temperature was normal, the urine was normal. There is no evidence, so far as I can see, although we have no complete skeletal x-ray films, of generalized metabolic disease.

We have a definite possibility of an inflammatory condition. The patient had a pilonidal sinus, which is notoriously difficult to cure by operation, and there may have been a low-grade secondary infection persisting with involvement of the bone. Tuberculosis, I should think, can be ruled out. I have not seen anything suggesting that in the record or past history. The blood Hinton test was negative, that test, however, is sometimes negative with bone syphilis.

We then come down to some form of tumor, primary or metastatic. One primary tumor that does occur in this region is chordoma, which is frequently seen in the sacrum, although it may arise at the base of the skull, or any point in the spinal column. One should think of chondroma, Ewing sarcoma and ordinary osteogenic sarcoma, the last being relatively rare in this situation, however.

Metastatic tumors may have occurred from the rectum or cancer in any part of the body, although the patient was only nineteen, which is young for a primary carcinoma with metastases. This is not conclusive, however, because cancer does occur in the young. The only positive finding suggesting cancer is the mucus passed by rectum.

I do not see how one can rule out Ewing sarcoma.

I cannot make a diagnosis in this case. On the facts presented the most probable diagnosis is a chordoma, which is the most frequent tumor in this situation. I am probably wrong because this diagnosis seems so obvious and we know that all the cases that Dr Mallory puts up to us are problems. A chondroma is a second possibility, and the third is malignant lymphoma of some sort. I think that it is impossible to make a definite diagnosis without a biopsy.

CLINICAL DIAGNOSIS

Tumor of sacrum and coccyx, unspecified

DR SIMMONS'S DIAGNOSIS

Chordoma?

ANATOMICAL DIAGNOSIS

Benign giant-cell tumor of coccyx and sacrum

PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY The opinion on the ward was the same as Dr Simmons's that it was impossible to make a diagnosis without a biopsy. The patient was operated on, and a segment of the tumor removed. I believe that while we were attempting to make a frozen section, the surgeon went ahead with the resection of the lower portion of the sacrum and the coccyx. The tumor proved rather puzzling on frozen section, as such lesions often do. It consisted of a considerable amount of fibrous tissue in which there were spicules of osteoid and a large number of foreign-body giant cells. On the basis of the general appearance I thought that benign giant-cell tumor was the most probable diagnosis. When the better sections came through, we were in somewhat the same predicament as Dr Simmons. The picture varied from one area to another, the tumor was much more fibrous and had a good deal more bone formation than is usual with a benign giant-cell tumor. The picture in some places suggested a condition that we call fibrous dysplasia of bone. In other areas large foreign-body giant cells were numerous. We made a final diagnosis of benign giant-cell tumor, although the possibility that it should be classed as fibrous dysplasia still exists. I can remember one other case of benign giant-cell tumor of the spinal column that extended out into the soft parts and eventually spontaneously broke through the skin of the back. The diagnosis was made by biopsy, and following x-ray therapy the lesion disappeared almost miraculously fast. and

Addendum to Case 33041 * A sixty-nine-year-old farmer, previously treated for a chondroma of the popliteal space by excisional surgery, was readmitted to the hospital two weeks after discharge. He complained of severe pain and stiffness in the right knee that had steadily increased since operation.

To determine whether the pain and limitation of motion were bona fide and to estimate the range of motion of the knee joint when the factor of pain was eliminated, a manipulation was done under Pentothal anesthesia. The range of motion of the knee was from 90 to 170°—with an average of 80°—and was all that could be obtained without force.

After the manipulation, the patient complained that the knee was more painful than ever, and he held the knee at 150° and resisted motion in both directions. The x-ray films at that time showed a recurrence of the tumor. There were multiple areas of calcification in the posterior aspect of the joint. The patient became anxious and worried about "cancer" when he was advised that only amputation would relieve the pain and cure the tumor. He was sent home to think the matter over more thoroughly and to calm his fears.

He returned to the hospital for a third admission, eight weeks after the previous operation. He asked that the leg be amputated because the pain was even severer than previously and there was no motion in the knee joint, which he held at 115°. He objected to any attempt at passive motion. There was palpable induration of the joint capsule. The entire knee was acutely painful to palpation, especially over the joint line on both the medial and the lateral aspects.

Under nitrous oxide, oxygen and ether anesthesia, a mid thigh amputation was done nine weeks after the previous operation in which the original tumor had been removed from the popliteal space. Pathological study of the specimen showed a complete knee amputation sharply 10 cm. above the joint and 16 cm. below, with overlying muscle, soft tissues and skin. Posterior to the knee joint there was a firm cartilaginous, somewhat nodular, tumor mass measuring 6.5 by 5 cm. and extending posteriorly for 3 cm. Although the mass was firmly adherent to the head of the tibia, no direct connection of the growth was found, and it was likewise separated a few millimeters from the femoral head. The synovial wall was involved, a few small seedings were noted on the articular surface of the tibia and in the anterior synovial membrane, and even over the tip of the patella there was a 4-mm. seed (Fig. 1). The

popliteal artery and vein were free of involvement. Section through the tumor proper revealed a fairly homogeneous cartilage, with a few small, soft, brown areas and foci of hemorrhage. The surface of the

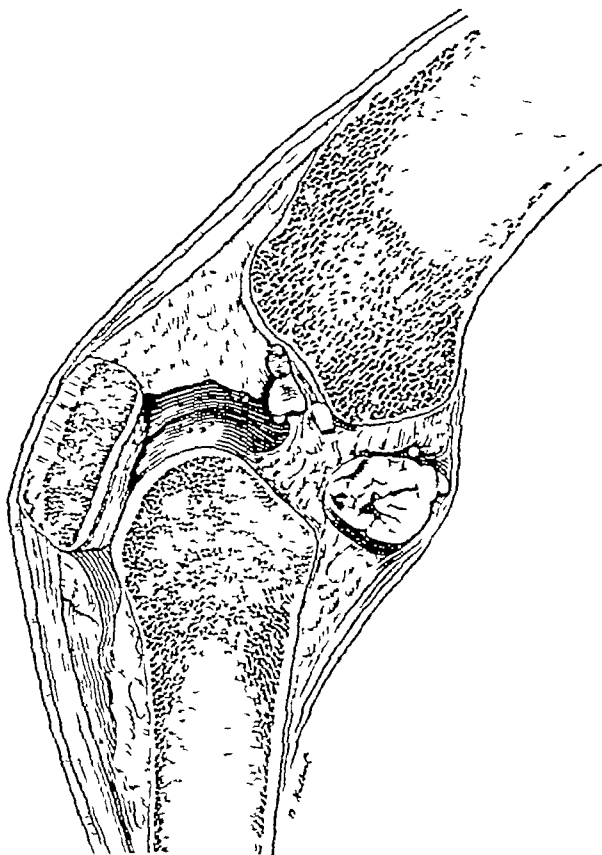


FIGURE 1

tumor was smooth but without a definite capsule. There was a small amount of red marrow on the head of the tibia, but otherwise it was fatty.

The tumor was composed of many large and small separate islands of well differentiated cartilage, with few cells and abundant hyaline matrix. Nearly all the islands were surrounded by narrow borders of myxomatous tissue that in places showed suggestive patterns of transition into cartilage. It was not possible to be certain whether this myxomatous tissue represented part of the neoplasm or a metaplastic process in the surrounding synovia. Although the usual histologic features of cancer were largely lacking, the infiltrative character and the rapid recurrence justified a diagnosis of chondrosarcoma.

The patient was discharged with an artificial limb. The stump was painless and functioned well.

MARSHALL R. URIST, M.D.

*Case Records of the Massachusetts General Hospital (Case 33041).
S. L. J. Med. 236:145-148, 1947.

tained 25 red cells and 15 white cells per high-power field. There was some albumin. I assume that that may not have been a catheterized specimen, because no attention seems to have been paid to it. If it had been a catheterized specimen, it seems to me that one would have to investigate further, at least to the extent of a pyelogram or some other investigation of the genitourinary tract.

Could this have been a metastasis from a primary neoplasm of the genitourinary tract? It had been present for three years. In that time the patient should have had symptoms referable to the kidneys or bladder. I therefore think that we must concentrate on the notion that this was a primary tumor. The results of x-ray treatment in the past argue a little more in behalf of a malignant than of a benign tumor, but the long course and the excellent health are more in favor of benign than malignant tumor. We can bet our money and take our choice. The fibromas, fibrosarcomas and periosteal fibrosarcomas seem to share the properties of soft parts and bone, and give rise to considerable soft-part tumors with less extensive bone involvement than occurs with osteogenic sarcoma or Ewing tumor or some of the other primary bone tumors. Chondromas and chondrosarcomas are likely to show evidence of bone formation or calcification within the tumor and to be lobular on palpation and on x-ray study of the soft-tissue swelling. We have had a certain number of synoviomias, but they are usually highly malignant, and rapidly growing. They may occur in this region not immediately in a joint but more or less removed from the joints and skeletal structure. Some of the ones we have seen here have given some indication of calcification. I do not see any evidence of calcification in this tumor.

Finally, we come to the group of lymphoblastic tumors that may involve bone and present soft-tissue tumors that respond gratifyingly to x-ray therapy. It is interesting that on physical examination no reference was made to the character of the skin in the axilla after two courses of x-ray therapy. It seems that that point might be relevant, because it would give some indication of the amount of x-ray treatment that had been given to relieve symptoms and perhaps to make the tumor disappear.

There are other rarer tumors that we can allude to simply for the sake of completeness, but I do not believe that we can make a diagnosis. We are confronted with a mass that involved the bone, and we shall have to resort to immediate pathological examination, the decision regarding the character of the tumor depends on the result of such examination. I favor a periosteal fibrosarcoma as a likely diagnosis, but it is anybody's guess.

DR NORMAN J. WILSON: I might add that this woman insisted that the tumor in her opinion had decreased with each course of x-ray therapy except the last, which had been inadequate. She had

definite relief of pain. Just how much the tumor decreased we could not tell because we had only the patient's word for it. It did not disappear entirely, however, because she was always able to feel it and was conscious of its presence.

DR TAYLOR: That should help me, but it does not.

DR TRACY B. MALLORY: Will you describe the operation, Dr. Wilson?

DR WILSON: We biopsied this tumor preoperatively and waited for the report before proceeding with treatment. We had considerable difficulty getting at the tumor. On the first attempt, we found a well encapsulated structure and took three good pieces of tissue from what we thought was tumor but discovered to be nothing but muscle overlying the tumor, the muscle had evidently been heaped up there as a result of reaction around the tumor and of the x-ray treatment. We were forced to make a larger incision and even then had considerable difficulty in getting a satisfactory biopsy. Dr. McKittrick resected the scapula below the spine along with the tumor en masse. At operation, when we approached the tumor we could not determine whether it was attached to the scapula anywhere, and the scapula to all intents and purposes was normal.

CLINICAL DIAGNOSIS

Fibrosarcoma of axilla?

DR TAYLOR'S DIAGNOSIS

Periosteal fibrosarcoma

ANATOMICAL DIAGNOSIS

Fibromyxosarcoma

PATHOLOGICAL DISCUSSION

DR MALLORY: The biopsy that was finally taken on this patient showed a neoplasm that we described as a fibromyxoma. After the resection and further sections we qualified that slightly and decided to call it a slowly growing fibromyxosarcoma. It was on the borderline of malignancy and well circumscribed but not completely encapsulated. Since we were unable to make out any point of true attachment to the scapula or its periosteum we thought that it was a tumor of the soft parts, with secondary erosion of the scapula, which is the other possibility that Dr. Taylor mentioned.

DR TAYLOR: I should have said — and meant to say — that, having argued against neoplastic disease on the grounds that this patient was in excellent health, I finally made a diagnosis of a type of malignant process that is frequently slowly growing in its propensity to spread and does not impair the patient's general condition for a long while — namely, a periosteal fibrosarcoma.

suggests that medical students should receive training in sex relations, on the basis of the average physician's inadequate equipment in this field, and undoubtedly he is right. At least the student would be made to realize the importance of the subject, and that it is in his province if he really wishes to make of himself the wise counselor that he should be. One difficulty, however, is that scientific knowledge is increasing by leaps and bounds, that the medical curriculum is already overloaded and that each department chronically needs more time in which to deliver its fundamental message.

Perhaps the curriculum of the average school is not now well planned, undoubtedly there is too much obstetrics for the future ophthalmologist, too much orthopedics for the embryonic laryngologist, too much surgery for the potential psychiatrist. The medical school, after all, can turn out only a doctor of medicine, not a physician or a surgeon, a dermatologist, an allergist or a pediatrician. The duty of the school, as it sees itself, is to impart basic principles and to give the student at least a speaking acquaintance with the various specialties of medicine and surgery. The medical school does not so much take the student onto a high place and point out the promised lands spread before him as it takes him into a broad valley from which he can see the peaks that challenge him to climb. The graduate himself, by his own efforts, having seen the range spread out in panorama before him, must essay the trail that will take him to his chosen peak.

Dr. Oliver Wendell Holmes, just seventy-five years ago last March, delivered a valedictory address to the graduating class of Bellevue Hospital College. His title was "The Young Practitioner," and his thesis, the theory — not altogether new — that the young graduate, bursting with knowledge, was not really a physician until he had gone through a depleting process to get rid of his extra medical-school learning and had replaced it with the fruits of experience. "Hard work," counseled the Autocrat, "will train it off, as sharp exercise trains off the fat of a prize-fighter." And again, from the same source, "Knowledge that is not wanted dies out like the eyes of the fishes of the Mammoth Cave."

Some knowledge of sex-counseling should undoubtedly be imparted to each candidate for the medical degree, even for his own sake, just as he is

required to have at least a smattering of ignorance on the mechanics of the birth of twins. Nothing, however, will make the student a good physician in this or in other matters unless he wishes to transmute his information into the right type of wisdom. "If you ship a poor cask of wine to India and back," said Dr. Holmes in 1871, "if you keep it half a century, it only grows thinner and sharper."

NEW ENGLAND DIABETES ASSOCIATION

ALTHOUGH insulin has been in use for over twenty-five years, the number of deaths attributed to diabetes continues to increase, and the disease ranks eighth among the leading causes of death in the United States. The New England Diabetes Association, a notice of whose organization meeting on April 16 appears elsewhere in this issue of the *Journal*, is an outgrowth of occasional informal gatherings held, for several years before the outbreak of World War II, by a group of physicians interested in the growing problem of diabetes as a disease affecting a sufficient proportion of the population to be considered a matter of concern to the community at large.

The purpose of the new association is to afford physicians, dietitians, nurses and other scientific workers especially interested in the welfare of diabetic patients an opportunity to meet regularly for discussion of the manifold problems of the diabetic patients in New England, conservatively estimated to number 80,000. Similar organizations have been of great value in the treatment of heart disease, tuberculosis, cancer and the arthritides. The formation of the New England Diabetes Association occurs at a time when the United States Public Health Service, with which it has no direct connection, is displaying an active interest in diabetes as a public-health matter. Physicians generally and specialists in diabetes in particular will welcome the efforts of the new organization.

MASSACHUSETTS MEDICAL SOCIETY BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups, such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of dates can be avoided.

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

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PUBLIC-HEALTH SERVICES IN MASSACHUSETTS

THE shortage in trained professional workers has created a critical situation in the Massachusetts Department of Public Health and Department of Mental Health and in many municipal health departments in the Commonwealth. At the present time these departments are operating under the handicap of a greatly reduced personnel, including physicians, nurses and other workers. For instance, in the Department of Public Health about 50 per cent of the positions filled by physicians and 40 per cent of those occupied by hospital workers are now vacant. Unless remedial steps are soon taken, the vital health services of these departments will be seriously impaired.

The shortage of physicians has been brought about, to a large extent, by the existing low-salary levels. The present scale of salaries of physicians in the service of the Commonwealth is considerably below those of the federal government and of many states. In fact, Massachusetts ranks thirty-eighth among the states in the average salary levels of public-health physicians. As a result there has been a continuous loss of capable men, attracted elsewhere by more lucrative positions in the federal and state services or in general practice, and a corresponding inability to fill these vacancies with well trained men, since inadequate salaries preclude competition with other agencies.

At its February meeting, the Council of the Massachusetts Medical Society, recognizing the gravity of the situation, voted to instruct the Committee on Legislation to give its support to an active program for raising the salary levels of physicians and other professional workers in the services of the Commonwealth or one of its political subdivisions. The Society considers that the scale of salaries in these state and local departments should be placed at levels that will allow Massachusetts to compete with outside agencies for the services of properly trained persons. In brief, the establishment of salaries on a competitive level appears to be the most logical and practical step for correcting the present unfortunate situation.

" TO GROW IN WISDOM "

THE part that the doctor should play in marriage counseling and in sex instruction was the subject of a talk given recently before the Planned Parenthood League of Massachusetts by Dr. James C. Janney, president of the Marriage Study Association. Dr. Janney's belief that many marriages are wrecked because of a lack of understanding and of good judgment in sex matters will be accepted by anyone who has given the subject any thought, and it must be equally apparent that the physician should be the one best equipped to give advice on the subject.

How the physician should acquire such knowledge, however, and how he can be interested in accepting what is clearly a professional obligation are difficult questions to answer directly. Dr. Janney

Malana was reported from Boston, 2, Cambridge, 1, Springfield, 1, Taunton, 1, Williamstown, 1, Worcester, 1, total, 7

Meningitis, meningococcal, was reported from Agawam, 1, Boston, 2, Framingham, 1, Greenfield, 1, Lowell, 1, Mansfield, 1, Newton, 1, Norton, 1, total, 9

Meningitis, Pfeiffer-bacillus, was reported from Brockton, 1, Everett, 1, Northampton 1, total, 3

Meningitis, pneumococcal, was reported from Beverly, 1, total, 1

Meningitis, other forms, was reported from Boston, 1, total, 1

Meningitis, undetermined, was reported from Haverhill, 1, Pittsfield, 1, Sterling, 1, Watertown, 1, total, 4

Pohomyelium was reported from Fall River, 1, Lowell, 1, New Bedford, 1, Saugus, 2, total, 5

Salmonellosis was reported from Arlington, 1, Belmont, 4, Boston, 2, Gardner, 1, Salem, 1, Uxbridge, 1, Weymouth, 1, Worcester, 2, total, 15

Septic sore throat was reported from Amesbury, 1, Belmont, 1, Boston, 6, Greenfield, 1, Haverhill, 1, Lynn, 1, Medford, 2, Merrimack, 2, Quincy, 1, Reading, 1, Salem, 1, total, 18

Trichinosis was reported from Cambridge, 2, Dighton, 1, total, 3

Typhoid fever was reported from Beverly, 1, Boston, 1, North Adams, 1, total, 3

Undulant fever was reported from Boxford, 1, Dudley, 1, Worcester, 1, total, 3

BOOK REVIEWS

Hazzell's Textbook of Physiology. Edited by John F. Fulton, M.D., Sterling Professor of Physiology, Yale University School of Medicine. Fifteenth edition 8°, cloth, 1304 pp., with 507 illustrations. London W. B. Saunders Company, 1946 \$8.00

It is a point of much importance that the distinguished Sterling Professor of Physiology at Yale University School of Medicine has undertaken to edit the fifteenth edition of this work, which has been a pacemaker of the subject in this country since its first appearance in 1905. This book, in which functional mechanisms are constantly brought into sharp focus, will be welcomed alike by students and physicians.

The ten sections of the volume include contributions by eminent authorities in their respected fields. Initially, the reader is presented with a brief, concise and thoroughly interesting chapter "Historical Backgrounds of American Physiology" by Dr. Fulton. The titles and the authors of the other sections are as follows: "Principles of Nervous and Muscular Activity," by David P. C. Lloyd; "The Central Nervous System Motor functions," by John F. Fulton; "The Nervous System Sensory functions," by Theodore Roch; "Properties and Constituents of the Blood," by David I. Hitchcock; "Physiology of the Organs of Circulation of the Blood and Lymph," by Donald H. Barron; Harold Lampert and John F. Fulton, "Respiration," by Leslie F. Nims; "Body Fluids and Kidney," by Robert W. Clarke; "Physiology of Digestion and Secretion of the Alimentary Tract," by George R. Cowgill; "Metabolism and Nutrition," by John R. Brobeck; and "Physiology of Reproduction," by William U. Gardner.

This book contains fifty-six chapters. At the end of each chapter there are a number of excellent references. The editor and his collaborators have presented their material in a clear style, offering the complexity of detail and the fluidity of ideas that characterize present-day physiology in a manner that leaves little room for criticism of the authors for the omission of this or that particular subject matter. This book is a refreshing product at the hands of critical scholars and is sure to be of real service to all who study it.

The Bacterial Cell In its relation to problems of virulence, immunity and chemotherapy. By René J. Dubos. With an addendum by C. F. Robinow. 8°, cloth, 460 pp., illustrated. Cambridge, Massachusetts Harvard University Press, 1945 \$5.00

This book, a Harvard University Monograph in Medicine and Public Health, is a thoroughly documented expansion of a series of eight lectures delivered in 1944 at the invitation of the Lovell Institute in Boston. The Institute, managed

by a single trustee, has long deserved an enviable reputation for its wise and happy choice of lecturers. In selecting Dr. Dubos at that time George Fabyan Professor of Comparative Pathology and professor of tropical medicine, Schools of Medicine and Public Health, Harvard University, and also a member of the Rockefeller Institute, the high requirements have been fully met — thorough familiarity with the field of knowledge, demonstrated ability in original basic research, and a capacity for lucid exposition. An illustration of the author's philosophic temper is his choice of the quotations that head chapters and sections. In source, these "texts" range from St. Paul's "Epistle to the Corinthians" to Lewis Carroll and include aphoristic selections from Bacon, Bernard, Cohn, Ehrlich, von Liebig, Pasteur, Renan, Rousseau and Shelley.

The first chapters deal with the complexity of bacterial cells as revealed by direct cytologic examination and reaction to stains. Capsules, flagella, granules, nuclear structures, spores, cell division and colonial characteristics are discussed, with particular attention to their relation to pathogenicity. Revelations provided by electron micrographs are elaborated in the addendum by C. F. Robinow, of Cambridge, England.

Enzymic reactions contribute something to knowledge of bacterial structures. The nature, number and sometimes the architectural location of bacterial antigens have been profitably studied via the action of bacteriophages and the application of serological analysis, especially in connection with pneumococci and *Salmonella*.

Bacterial variations are considered, on admittedly inadequate evidence, to be probably ascribable to some selective process operating on forms originally present in the parental culture. Concerning the transformation of pneumococcal types, however, it appears that a real genetic mutation is induced by a highly polymerized deoxyribonucleic acid. If the strong evidence upholding this concept turns out to be valid, its discoverers (Avery, MacLeod and McCarty) have made a fundamental contribution that is likely to have wide and profound scientific applications.

The illuminating discussion of virulence and its intricate nature, in terms of modern concepts, is not equaled in any publication that the reviewer has seen. The importance of the host is considered, but Dubos's analysis of infection deals more with antigenic structure, toxins, variations and adaptations. Recognition that virulence is a complex quality and that modification or loss of only one of its components (each readily capable of independent variation) may abolish pathogenicity has the effect of multiplying the points of vulnerability of harmful micro-organisms, thus in turn affords a correspondingly increased number of mechanisms with which antibiotic agents may effectively interfere. In the discussion of immunization against infections and in nearly sixty pages given over to bacteriostatic and bactericidal agents this conception is expanded in relation to the multiplicity of immunochemical structures and specificities of cellular components, as well as the intimate nature of such metabolic processes as nutrition, respiration, growth and division.

Most studies of antibiosis have emphasized the effect of various agents on catabolic reactions, but there are a few cases in which it seems that the essential primary effect of the inhibition is on a synthetic anabolic process vitally necessary to bacterial activities. Wider and more detailed studies of bacterial physiology and nutrition are highly desirable, that chemotherapy may advance more logically and rapidly. The mechanisms of drug-fastness receive detailed consideration. The final chapter on trends and perspectives deals chiefly with the nature of specificity and the significance of bacterial variability.

The bibliography comprises about a thousand titles, the text page on which the citation is discussed is also indicated — an especially helpful feature that should be widely copied. Type and presswork are excellent.

Least all these comments be deemed too uniformly fulsome, the reviewer protests against the use of "haptene." This spelling is probably a mere upshoot from the author's Gallic origin, but it is a retrogressive step toward "toxine," "agglutinine" and so forth, current within the reviewer's memory, and it is an unwarranted meddling with Landsteiner's neologism "haptene."

This is an important book — crucial, penetrating, informative stimulating and, especially, heuristic. Despite the existing primitive and fragmentary knowledge or complete

DEATHS

DOLE — Mary P. Dole, M.D., of Shelburne, died February 23. She was in her eighty-fifth year.
Dr. Dole received her degree from Woman's Medical College of Baltimore in 1888.
Several nieces and nephews survive.

GIGGER — Augustus G. Gigger, M.D., of Falmouth, died November 27. He was in his sixty-ninth year.
Dr. Gigger received his degree from Boston University School of Medicine in 1906.

JENNINGS — John G. Jennings, M.D., of Weston, died February 17. He was in his fifty-ninth year.
Dr. Jennings received his degree from Tufts College Medical School in 1915. He was a member of the staff of the Massachusetts Eye and Ear Infirmary and of the Waltham Hospital, as well as a member of the New England Ophthalmological Society and a fellow of the American Medical Association.
His widow, a daughter and a son survive.

KEES — Philip A. Kees, M.D., of West Springfield, died November 4. He was in his thirty-ninth year.
Dr. Kees received his degree from University of Minnesota Medical School in 1936. He served as a medical officer in World War II, receiving the Purple Heart, The Bronze Star for valor and the Silver Star for gallantry in action. He was a fellow of the American Medical Association.
His widow and three children survive.

SEDGLEY — Frank R. Sedgley, M.D., of Redwood City, California, died February 12. He was in his sixty-eighth year.
Dr. Sedgley received his degree from Boston University School of Medicine in 1902. He was a fellow of the American College of Surgeons and the American Medical Association.
His widow survives.

SMITH — Roswell H. Smith, M.D., of Edgartown, died February 12. He was in his fifty-third year.
Dr. Smith received his degree from Middlesex University School of Medicine in 1922.
His widow and two daughters survive.

TYNAN — Joseph P. Tynan, M.D., of South Boston, died recently. He was in his sixty-third year.
Dr. Tynan received his degree from Tufts College Medical School in 1910.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

SHORTAGE OF CONTAINERS FOR BIOLOGIC PRODUCTS

The shortage of containers for serum, vaccines and blood products is at present more critical than ever, and deliveries of new supplies cannot be expected in less than five or six months. A further complication arises from the great increase in the demand for biologic products. During the past six months distribution of certain products has increased, as against one year ago, to the following extent: diphtheria antitoxin, 94 per cent, diphtheria toxoid, 160 per cent, Schick outfits, 159 per cent, typhoid vaccine, 47 per cent, and immune serum globulin, 303 per cent. Distribution of plasma begun in March, 1946, has totaled 16,748 units, and 4458 pints of whole blood have been issued since May, 1946, when this service was begun.

The Department of Public Health cannot maintain the present rate of distribution unless empty containers or unused products of all types are re-

turned. Blood bottles in particular represent a considerable expense to the Commonwealth, and their prompt return is essential if this service is to be continued. Physicians, hospitals and health agencies are most urgently asked to co-operate with the Department in the present emergency, as they did so outstandingly during the war, by returning as many containers as possible, either to local board-of-health depots, to district health offices or directly to the Division of Biologic Laboratories. When other transportation cannot be arranged, large shipments may be sent express collect to the Division of Biologic Laboratories, 375 South Street, Jamaica Plain. For detailed arrangements or information telephone ARNold 4127.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JANUARY, 1947

DISEASES	RÉSUMÉ		
	JANUARY 1947	JANUARY 1946	SEVEN YEAR MEDIAN
Chancroid	1	3	3*
Chicken pox	2,391	1,023	1,798
Diphtheria	77	10	14
Dog bite	522	487	511
Dysentery, bacillary	10	4	6
German measles	108	73	130
Gonorrhea	360	663	357
Granuloma inguinale	1	0	0*
Lymphogranuloma venereum	1	1	1*
Malaria	7	52	1018
Measles	1,885	1,018	18
Meningitis meningococcal	9	24	18
Meningitis Pfeiffer-bacillus	3	3	7†
Meningitis pneumococcal	1	7	0†
Meningitis, staphylococcal	0	0	0†
Meningitis, streptococcal	0	1	2†
Meningitis, other forms	1	3	5†
Meningitis, undetermined	4	4	913
Mumps	666	698	390
Pneumonia, lobar	142	325	2
Poliomyelitis	5	0	5
Salmonellosis	13	5	1,200
Scarlet fever	659	804	417
Syphilis	311	617	213
Tuberculosis pulmonary	277	5	17
Tuberculosis, other forms	15	0	2
Typhoid fever	3	1	2
Undulant fever	3		
Whooping cough	895	480	625

*Three-year median

†Five-year median

COMMENT

Interest in communicable diseases continues to focus on the increased prevalence of diphtheria. The number of cases reported in January is nearly eight times the number in the same month in 1946, and more than five times the seven-year median. Boston and New Bedford, which have had an increased prevalence during the last three years, continued to report the bulk of the cases. The disease appears, however, to be spreading into the Connecticut Valley, and an upward trend can be expected in that area unless immunization procedures are redoubled.

Other diseases above the seven-year median for the month were chicken pox, bacillary dysentery, measles, poliomyelitis, salmonellosis, pulmonary tuberculosis and whooping cough.

Among the diseases below the seven-year median were meningococcal meningitis, mumps, lobar pneumonia and scarlet fever.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Boston, 30, Brookline, 1, Cambridge, 1, Chelsea, 8, Clinton, 1, Everett, 2, Fall River, 1, Greenfield, 2, Holyoke, 1, Ipswich, 1, Lowell, 3, Lynn, 2, New Bedford, 12, Palmer, 2, Randolph, 1, Somerville, 4, Springfield, 2, Stoughton, 1, Wayland, 1, West Bridgewater, 1, total, 77.

Dysentery, amebic, was reported from Boston, 1, total, 1.
Dysentery, bacillary, was reported from Salem, 1, Worcester, 5, Wrentham, 4, total, 10.

The New England Journal of Medicine

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Volume 236

APRIL 10 1947

Number 15

THE USE OF CURARE IN ANESTHESIA*

EDWARD C. ALLEN, M.D.,† AND URBAN H. EVERSOLE, M.D.‡

BOSTON

FOR the past few centuries, curare has been dismissed lightly as being synonymous with the generic name of several arrow poisons of certain South American Indians, but investigation of its pharmacologic action and clinical application in the past decade has shown this drug to hold great promise to the anesthesiologist. The first descriptions of this so-called "arrow poison" were brought back to the civilized world by Sir Walter Raleigh in 1595 following his journey to Guiana and up the Orinoco.¹ Because of the variable source and potency of the drug and because of the toxic effects due to the impurities in the crude preparations, little advance was made in its investigation until the researches of the eminent physiologist Claude Bernard on its use in hydrophobia, chorea, tetanus and epilepsy. From his work came the first realization that the physiologic action of curare takes place at the myoneural junction.

Full credit for the modern development of curare must be given to Gill,¹ who spent much time in the Amazonian jungles and in 1938 brought back to this country adequate supplies of the drug for investigative work. From that time on there has been no standstill in research on the properties of this drug. Gill² recently cleared up what he considered misconceptions about the source and development of the drug. He stated that curare is not derived from a single species of plants but is a mixture of botanical components, widely distributed throughout northern and western South America, more particularly in regions of Amazonian drainage. The type of primitive container, whether it is a bamboo tube or gourd, bears no relation to the type of curare it contains.

McIntyre³ and Bennett,^{4, 5} at the University of Nebraska, conducted the first modern pharmacologic study and clinical trial of the drug. It was first used in the field of psychiatry in an attempt to overcome some of the less desirable accompaniments of convulsive shock therapy. To Griffith

and Johnson,⁶ of Montreal, goes the credit for the introduction of curare to the field of anesthesiology in 1942. They reported the effectiveness of this drug in producing muscular relaxation in patients anesthetized with cyclopropane. Numerous reports of the successful use of curare to enhance muscular relaxation in conjunction with all types of general anesthetics were subsequently made.⁷⁻¹⁵

Intocostin§ — a standardized product of greater purity — has been available since 1940. It is a clear, amber-colored solution supplied in rubber-stoppered vials containing 20 mg. of the crude drug per cubic centimeter. It is biologically assayed and tested in man before being distributed. It is sufficiently free of hydrolyzable resins so that it is not subject to clouding for at least a year if kept refrigerated. Little has been mentioned in the literature concerning its chemical nature, although it has been said to resemble bisbenzylisoquinoline alkaloid.¹⁶ It is best administered intravenously but can be given intramuscularly, allowance for the time interval for effective action being made. Intocostin is nonirritating to tissues even when given subcutaneously.

The primary site of physiologic action of curare is peripherally at the myoneural junction. The exact nature of this mechanism is not completely understood. The muscle response to the acetylcholine influence at the myoneural junction is markedly diminished either by an increase in the threshold of reaction to the normal concentration of acetylcholine or by a sort of neutralization of the acetylcholine activity. Regardless of the mechanism, the result of administration is a paresis or paralysis of the voluntary musculature throughout the body. There is a progressive action on muscle groups starting with the head and neck and extending downward to the trunk and extremities and lastly to the muscles of respiration. Fortunately, the diaphragm is the last muscle to be affected. There seems to be a paresis first in the short muscles of the head supplied by cranial nerves and then the longer muscles of the neck, trunk and extremities.

*From the Department of Anesthesiology, Lahey Clinic.

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§Obtainable from E. R. Squibb and Sons, New York City.

ignorance of many essential factors, the author has succeeded remarkably in integrating and interpreting information drawn from many fields and pertinent to the biochemical architecture of micro-organisms

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Renal Hypertension By Eduardo Braun-Menéndez, Juan Carlos Fasciolo, Luis F. Leloir, Juan M. Mumoz and Alberto C. Taquini, Institute of Physiology, Faculty of Medical Sciences, and Institute of Cardiology, V. F. Grego Foundation, Buenos Aires, Argentina. Translated by Louis Dexter, M.D. Harvard Medical School and Peter Bent Brigham Hospital. 8°, cloth, 451 pp., with 90 illustrations. Springfield, Illinois: Charles C. Thomas, 1946. \$6.75.

Ambulatory Proctology By Alfred J. Cantor, M.D., associate proctologist, Kew Gardens General Hospital, Long Island, New York. With a foreword by Beaumont S. Cornell, M.D., editor, *American Journal of Digestive Diseases*. 8°, cloth, 524 pp., with 281 illustrations. New York and London: Paul B. Hoeber, Incorporated, 1946. \$8.00.

Handbook of Neurological Examination and Case Recording By D. Denny-Brown, M.D., James Jackson Putnam Professor of Neurology, Harvard Medical School. 12°, paper, 112 pp. Cambridge, Massachusetts: Harvard University Press, 1946. \$1.75.

Penicillin: Its practical application Under the general editorship of Sir Alexander Fleming, M.D., B.S., F.R.C.P., F.R.C.S., F.R.S., professor of bacteriology in the University of London, St. Mary's Hospital, London. 8°, cloth, 380 pp., with 59 illustrations. Philadelphia: Blakiston Company, 1946. \$7.00.

Introduction to Surgery By Virginia Kneeland Frantz, M.D., assistant professor of surgery, Columbia University College of Physicians and Surgeons, associate attending surgical pathologist, Presbyterian Hospital, New York City, and Harold Dornic Harvey, M.D., assistant professor of clinical surgery, Columbia University College of Physicians and Surgeons, assistant attending surgeon, Presbyterian Hospital, New York City. 12°, cloth, 216 pp. New York: Oxford University Press, 1946. \$2.50.

Myasthenia Gravis By Dr. Adalberto R. Goni, member of the staff of the Hospital Alvear, Buenos Aires, chief, Medical Clinic of the Sanitary Service of the Post Office, Telephone and Telegraph. Translated by Georgianna Simmons Gittinger. 8°, cloth, 112 pp., with 10 illustrations. Baltimore: Williams and Wilkins Company, 1946. No charge.

Lippincott's Quick Reference Book for Medicine and Surgery: A clinical, diagnostic and therapeutic digest of general medicine, surgery and the specialties, compiled systematically from modern literature By George E. Rehberger, M.D. Thirteenth edition. 4°, cloth, 1461 pp., with 302 illustrations. Philadelphia: J. B. Lippincott Company, 1946. \$15.00.

Western Reserve University Centennial History of the School of Medicine By Frederick C. Waite, A.M., Ph.D. 8°, cloth, 588 pp., with 15 illustrations and frontispiece. Cleveland: Western Reserve University Press, 1946. \$6.00.

NOTICES

JOSEPH H. PRATT
DIAGNOSTIC HOSPITAL

Bennet Street, Boston
Lecture Hall, 9-10 a.m.
MEDICAL CONFERENCE PROGRAM

Wednesday, April 9 — Functional Tests in the Diagnosis of Pancreatic Disease. Dr. Martin Nothmann.

Friday, April 11 — Di-isopropyl Fluorophosphate in its Control of Glaucoma. Dr. Edwin B. Dunphy.

Wednesday, April 16 — Clinicopathological Conference. Drs. Robert Williams and H. E. MacMahon.

Friday, April 18 — Studies in Histochemistry. Dr. Henry Bunting.

Wednesday, April 23 — Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon.

Friday, April 25 — Temporal Arteritis. Dr. Roy C. Crosby.

Wednesday, April 30 — The Relation of Enzyme Chemistry to Some Recent Advances in Chemotherapy. Dr. Gerhardt Schmidt.

On Tuesday and Thursday mornings, Dr. S. J. Thannhauser will give medical clinics on hospital cases. On

Saturday mornings, clinics will be given by Dr. William Dameshek. Medical rounds are conducted each weekday by members of the staff from 12:00 to 1:00 in the Lecture Hall. All exercises are open to the medical profession.

NEW ENGLAND DIABETES ASSOCIATION

The first meeting of the New England Diabetes Association will be held on Wednesday, April 16, at 7:30 p.m., in the Dowling Amphitheater, Boston City Hospital.

PROGRAM

Diabetes and Hyperthyroidism. Drs. Frank N. Allan and Rosemary Murphy.

The Relation between Insulin Sensitivity and Insulin Resistance. Dr. Francis C. Lowell.

Diabetic Coma at the Boston City Hospital. Dr. W. R. Ohler.

Renal Disease in Diabetes. Dr. Stanley Robbins.

A brief business meeting for the purpose of electing officers and directors and adopting a constitution, will follow.

Physicians, surgeons, nurses, dietitians and other scientific workers interested in the problems of diabetes may apply for membership at the meeting or may write for application blanks to the temporary secretary, Dr. James H. Townsend, 330 Mt. Auburn Street, Cambridge.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, APRIL 10

FRIDAY, APRIL 11

*9:00-10:00 a.m. Di-isopropyl Fluorophosphate in its Control of Glaucoma. Dr. Edwin B. Dunphy. Joseph H. Pratt Diagnostic Hospital.

*10:00 a.m.-12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

12:00 m.-1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

MONDAY, APRIL 14

*12:15-1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, APRIL 15

12:00 m.-1:00 p.m. Dermatological Service, Grand Rounds. Amphitheater, Dowling Building. Boston City Hospital.

*12:15-1:15 p.m. Clinicoradiological Conference. Peter Bent Brigham Hospital.

(Notices continued on page xvii)

tory in some cases in which actual laryngeal spasm occurs as a result of inadequate general anesthesia used coincidentally with the injection of curare Knight,²⁴ on the other hand, has found curare to be practically specific in cases in which laryngeal spasm develops during anesthesia. This point is still quite controversial.

In patients in whom shock is present or appears imminent, and in elderly or debilitated patients, it is wise to use smaller doses than are ordinarily employed.

Cyclopropane appears to be the ideal anesthetic agent to be used in combination with curare. The patient is carried in a light plane (usually the second) of anesthesia throughout. Curare neither increases nor decreases the irritability of the heart when employed with cyclopropane. This combination affords a pleasant and rapid induction and recovery with no aftereffects, and its most ardent supporters believe that the relaxation compares favorably with that obtained with spinal anesthesia.

Curare has been used with both the weaker gases nitrous oxide and ethylene.²⁵ Neither of these alone is capable of causing good flaccid muscular relaxation, and yet the relaxation from its combination with curare is satisfactory for upper abdominal operations. Much larger doses of curare are employed with these gases than with the more potent anesthetic agents, and in some cases there has been marked respiratory depression.

When curare is used to supplement ether anesthesia, great precaution must be taken in its administration. Ether has been demonstrated to have an action similar to that of curare, so that the myoneural junction is already partially paralyzed. There is a sort of cumulative action so that all the effects of curare will be increased, especially the length of respiratory depression. Thus, it is advisable to use smaller doses of curare, either 20 or 40 mg, instead of the usual 60 mg. Several cases of severe circulatory depression after the combination of ether and curare have been reported. Cullen²⁶ stated that this curariform action is an attribute not only of ether but also of tribromethanol and Pentothal Sodium, especially when the blood concentration is high.

The recent literature contains favorable reports on the combined use of curare and Pentothal,²⁷ but again a word of warning is necessary. It must be remembered that with this combination two respiratory depressants are being used at the same time. Provided that the anesthetist is fully capable of dealing with any respiratory problem that may arise, — whether it is depression or obstruction, — there is no great danger in the combination. Pentothal and curare should not be given through the same needle because of the formation of a precipitate. Recent development of a crystalline product is reported to overcome this disadvantage. Experience has shown that the total dose of Pentothal

is definitely reduced when the drug is used in conjunction with curare and also that the period of postoperative narcosis is considerably shortened.

There are a few definite contraindications to the use of curare. It should not be administered when myasthenia gravis is present or when there exists the least possibility that the anesthetist will be unable to deal with the problem of artificial respiration. It probably should not be used in patients with suspected liver or renal impairment.

Although prostigmine is the direct antidote for curare, there have been no reports of its use even in cases in which large doses of curare were given and periods of apnea resulted. Treatment has consisted solely of artificial respiration.

Curare has proved to be a valuable adjunct to spinal anesthesia. This is true when a single-dose agent has produced anesthesia of insufficient duration for the completion of the operation. The total amount of spinal-anesthetic agent needed when the continuous technic is employed is often materially lessened by the administration of curare toward the end of the operation. This may be significant in view of the fact that there is considerable evidence that neurologic complications after a spinal anesthetic may bear a relation to the total amount of drug used.

Curare has been used to advantage in several abdominal operations for massive hemorrhage from gastric or duodenal ulcer in which the patient was bleeding profusely and was in a state of severe shock on arrival in the operating room. Since spinal anesthesia was contraindicated because of the marked hypotension, these patients were carried on cyclopropane and curare, a technic similar to that advocated by Cullen being used. The cyclopropane provided anesthesia with a sufficiently high oxygen concentration to prevent the development of hypoxia, and the curare provided adequate relaxation — almost equivalent to that of spinal anesthesia.

The use of curare in combination with Pentothal is becoming more extensive. Bronchoscopies and esophagoscopies are easily performed with this combination. The technic should include a thorough cocaineization of the pharynx and larynx before the administration of either drug. Curare is usually given while the patient is awake, the dosage depending on the age, size and vigor of the patient. The average dose is 60 mg. The effectiveness of the curare is determined by the patient's ability to raise his head or arms from the table. When this ability is impaired, the Pentothal is administered in the usual manner. When there is no impairment in ability to raise the head, it is evident that the dosage of curare is inadequate and a second dose is administered. This technic has obviated the necessity of deep ether anesthesia for difficult endoscopies and has appreciably shortened the time for these procedures.

Recovery from the paralysis of curare appears to be in the reverse order. With increased doses, the paresis of respiratory muscles may go on to complete paralysis. This is the one great danger in its use, particularly if facilities are not readily available to overcome it with effective artificial respiration. If curare is given to a conscious patient the results may be distressing to both the physician and the patient. The patient first notices diplopia or haziness of vision and weakness of the eyelids and then starts to salivate, only to find that he is unable to move his jaws, swallow or cough. This is followed by inability to raise the head, inability to move the extremities and, finally, difficulty in breathing. These symptoms are so distressing as sometimes to produce in the patient a fear of impending death. The administration of large enough doses of curare to conscious patients to cause these symptoms is unwarranted. The drug is supposed to have no central action, but further experimental work may disprove this assumption. Whitacre and Fisher¹⁷ have shown that patients can be made unconscious by exceptionally large doses of curare. Smith¹⁸ permitted the drug to be administered to him until complete respiratory paralysis had occurred and stated that he had not lost consciousness. Fegler¹⁹ demonstrated that curare affected the respiratory center in animals before the full development of its peripheral action. Stimuli that ordinarily increase or decrease the frequency and amplitude of respiration had no effect during the period of respiratory inhibition. For many years, crude curare was found to be extremely toxic to the cardiovascular system, but this has now been proved to have been the result of impurities in the preparation. There are no electrocardiographic changes in either normal or diseased hearts during curare administration, but it must be remembered that the respiratory depressing effect may be responsible for the production of apnea and hypoxia, which in turn may aggravate cardiac damage.²⁰ The hypotension seen after curare is transient. The pulse is unaffected, and the drop in the blood pressure is only about 20 mm of mercury and usually lasts for only a few minutes. It is questionable whether this is the result of a block in transmission between preganglionic and postganglionic fibers in the sympathetic system or of poor peripheral venous return resulting from the loss of muscle tone. Curare seems to produce a temporary loss of tone and peristaltic activity of the small bowel.²¹

A safety factor in the administration of curare is the rapidity with which it is eliminated from the body. Most of it is broken down in the liver, and the remainder is excreted unchanged by the kidneys.²²

Laboratory and clinical experiences have yet to prove certain actions of curare, such as its effect on involuntary muscles, placental permeability, blood and blood-forming tissue and also its effect on cells of the central nervous system. It is thought

that its action does not extend to structures innervated by postganglionic fibers, such as the glands and smooth muscle. At any rate, no permanent pathologic change has yet been demonstrated following its use.

Curare, a nonanesthetic and nonhypnotic drug, was introduced into the field of anesthesiology because of the excellent muscular relaxation that it provided. Far too frequently, the situation has arisen in the course of an operation when the surgeon's work is hampered because of the poor relaxation of the patient. The anesthetist in despair may deepen the anesthesia to a point that is physiologically unsound and definitely detrimental to the patient. This situation need no longer exist now that curare is available. This statement is not to be construed to mean that the drug is advised as an outlet or excuse for a poorly planned or poorly administered anesthetic. On the contrary, curare is advocated by Griffith and Johnson⁶ and by Cullen²³ in a planned technic of administration in combination with cyclopropane. This means that the anesthesia can be carried in a relatively light plane and still provide adequate relaxation. The technic consists of putting the patient to sleep in the usual manner with cyclopropane and giving the first dose of curare just as the skin incision is made. Griffith⁶ originally used 100 mg (units) practically routinely as the first dose, whereas Cullen²³ advised an average initial dose of 60 mg in patients from twenty to seventy years of age. After an interval of three to five minutes, if the initial dose is found to be inadequate, an additional dose of 40 mg is administered, and if this is also inadequate a third injection, one of 20 mg, is given. The initial dose may be sufficient if the operation does not last longer than forty-five minutes. If the procedure is longer, supplementary doses should be given, a half to a third the initial dose being used. The drug has been given to both young and old patients and to those who are both good and poor risks. In small infants dosages of from 4 to 6 mg have been employed. Experience has shown that an intravenous injection is usually effective in thirty to sixty seconds and lasts about twenty minutes. The total dosage given during an operation is not too important. There will be a return of adequate respiratory excursions long before the return of muscle tonus. The one factor that must be observed closely is the effect of each dose on the respiration.

As stated above, the anesthetist must definitely be prepared to treat respiratory depression or apnea. Poor respiratory exchange must not be tolerated for any length of time because of the likelihood that a hypoxic state and the accumulation of carbon dioxide will develop. Adequate airways must be available, and in fairness to the patient, the anesthetist should have some knowledge of the technic of endotracheal intubation. This, indeed, is manda-

experience, it was found to be more advantageous to begin the administration of curare as much as five to fifteen minutes before the time of expected relaxation. This early onset of administration allowed sufficient time for subsequent doses if required, and permitted another way of administering curare—namely, by repeated small doses. When curare is given in this manner, the anesthesiologist can more closely approximate the proper dose by evaluating the response of the patient to the repeated injections of the drug, rather than depending solely on an arbitrary standard dose administered at the beginning of the operation.

Although efforts were made to use the smallest dose, varying degrees of depressed respiration and respiratory paralysis were experienced in a number of cases. The relatively narrow margin between the optimal dose and that producing respiratory paralysis corresponded to that described by Cullen.⁹ It was found that before the respiratory impairment produced by the paralysis of the intercostal muscles and diaphragm, the respirations became depressed in varying degrees. This depression appeared in several cases when the abdominal muscles were not sufficiently relaxed. This phenomenon probably results from the depressant effect of curare directly on the respiratory center. As Fegler¹² demonstrated the drug influences the respiratory center before the full development of its peripheral action.

During the administration of curare, when the respirations became depressed and the excursions of the breathing bag perceptibly decreased the respiratory movements were immediately supported by the application of manual compression on the breathing bag, the minute volume exchange being thus increased. In many cases this support to the respiration was followed by periods of apnea with controlled breathing. It would be difficult to determine how often this apnea was primarily due to respiratory paralysis produced by curare or to the so-called "apneic technic." The return of spontaneous respiration occurred on the average in ten or fifteen minutes when the general anesthesia was lightened. Nevertheless, in several cases this return of spontaneous respiration did not occur so readily as in the straight apneic technic. Controlled breathing was probably used more frequently than was absolutely necessary. This procedure seems to be justified by the following supposition: owing to the many factors that have a depressant effect on the respiratory center during anesthesia¹³ and to the additional depressing effect of curare, proper oxygenation and carbon dioxide elimination are questionable with the patient's own depressed respiration, whereas they are assured with controlled breathing.

Controlled breathing is therefore a safety measure in cases of depressed respiration in which the sufficiency of the minute volume exchange can be questioned. It is an absolute necessity in cases of

respiratory paralysis in which spontaneous respiratory exchange has ceased. Since the need of establishing controlled breathing may arise at any time, curare should be administered only by those whose technical abilities as well as practical and theoretical knowledge of respiratory physiology guarantee uninterrupted and complete oxygenation and carbon dioxide elimination during periods of depressed respiration and apnea. Equally important is the proper functioning of the anesthesia machine and other anesthesia equipment used for controlled breathing.

The principles in this discussion of respiration apply not only to the cases in this group but also to any cases in which curare is used.

The second group included cases in which a single-dose spinal anesthetic for abdominal surgery was used. The surgical procedures in these cases lasted longer than was anticipated, and the effect of the anesthetic wore off at a time when relaxation was still required. Curare was used to provide relaxation.

The following method of administration was found to be the most satisfactory. Whenever there was any indication that the spinal anesthesia had started to wear off—or if there were no such indications but the expected duration of spinal anesthesia had been reached—general anesthesia was induced with either Pentothal or cyclopropane. The patients were maintained for the remainder of the operation in a light plane of the surgical stage of anesthesia. The administration of curare was begun five to fifteen minutes before the closure of the peritoneum, or earlier if the surgeon did not find sufficient relaxation on intra-abdominal manipulation. Curare was given in doses of 20 to 50 mg every three to five minutes until complete relaxation was obtained. The total amount administered to any one patient ranged between 50 and 160 mg.

Few changes in circulation were noticed following the administration of curare in the cases in this group as well as those in the first group. Only a few patients showed a moderate and transitory decrease in blood pressure. This favorable circulatory response led to the use of the drug in the cases in the following group.

The third group consisted of poor-risk patients requiring abdominal surgery. Many of them suffered from severe, acute blood loss following uncontrollable gastric hemorrhage, ruptured ectopic pregnancy or postoperative internal hemorrhage, and others were in shock owing to advanced abdominal disease, such as perforated peptic ulcer of more than one day's duration, generalized peritonitis or volvulus with gangrenous bowel.

These patients received light premedication. While intravenous fluids and, in most cases, transfusion were being administered, anesthesia was induced and maintained in the first plane of the third stage with cyclopropane. Abundant oxygenation

For more extensive operations, the combination of curare, Pentothal and nitrous oxide has been used, these include laminectomies, splanchnicectomies and more recently, intrathoracic operations. Since this combination eliminates the employment of inflammable agents, it permits the use of high-frequency electrosurgical apparatus in the chest. Induction is carried out in the same manner as in endoscopy. Subsequent doses of curare are given at intervals of twenty to thirty minutes, according to the need for relaxation at the time. It has been our observation that the total amount of Pentothal in these cases has been decreased. Needless to say, the patient's respirations must not be so depressed that he suffers from even transient hypoxia.

* * *

In the course of a few years, curare has proved itself to be of considerable value in the field of anesthesiology. It is not to be considered a panacea to answer all problems of relaxation, but it is certainly a useful adjunct. Further investigative research will no doubt augment its clinical applicability.

Since this paper was submitted for publication a solution of pure *d*-tubocurarine has become available. This preparation is biologically assayed so that its dosage is the same volume as that for Intocostarin.

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REFERENCES

1. Gill, R. C. *White Water and Black Magic* 369 pp. New York: Henry Holt & Company, Inc., 1940.
2. *Idem*. Curare: misconceptions regarding discovery and development of present form of drug. *Anesthesiology* 7: 14-23, 1946.

3. McIntyre, A. R., and King, R. E. *d*-Tubocurarine chloride and choline esterase. *Science* 97: 69, 1943.
4. Bennett, A. E. Preventing traumatic complications in convulsive shock therapy by curare. *J A M A* 114: 322-324, 1940.
5. *Idem*. Curare preventive of traumatic complications in convulsive shock therapy (including preliminary report on synthetic curare-like drug). *Am J Psychiat* 97: 1040-1060, 1941.
6. Griffith, H. R., and Johnson, G. E. Use of curare in general anesthesia. *Anesthesiology* 3: 418-420, 1942.
7. Smith, S. M. Curare as adjuvant during inhalation anesthesia. report of fifty cases. *Rocky Mountain M J* 41: 313-317, 1944.
8. Knight, R. T., and Baird, J. W. Anesthesia for aging and aged. *Journal-Lancet* 64: 183-185, 1944.
9. Waters, R. M. Nitrous oxide-oxygen and curare. *Anesthesiology* 5: 618, 1944.
10. Cullen, S. C. Use of curare in anesthesia. *South M J* 38: 144-148, 1945.
11. Griffith, H. R. Curare as aid to anesthesiologist. *Lancet* 2: 74, 1945.
12. *Idem*. Use of curare in anaesthesia and for other clinical purposes. *Canad M A J* 50: 144-147, 1944.
13. Cole, F. Use of curare in anesthesia: review of 100 cases. *Anesthesiology* 6: 48-56, 1945.
14. Cullen, S. C. Clinical and laboratory observations on use of curare during inhalation anesthesia. *Anesthesiology* 5: 166-173, 1944.
15. Everaale, U. H. Use of curare in anesthesia. *S Clin North America* 26: 709-714, 1946.
16. Wintersteiner, O., and Dutcher, J. D. Curare alkaloids from Chondrodendron tomentosum. *Science* 97: 467-470, 1943.
17. Whitacre, R. J., and Fisher, A. J. Clinical observations on use of curare in anesthesia. *Anesthesiology* 6: 124-130, 1945.
18. Smith, S. Personal communication.
19. Fegler, J. Action of curare on respiratory centre. *J Physiol* 100: 417-422, 1942.
20. Ruskin, A., Ewalt, J., and Decherd, G. M., Jr. Electrocardiogram of curarized human patients. *Dis Nerv System* 4: 335-341, 1943.
21. Gross, E. G., and Cullen, S. C. Action of curare on smooth muscle of small intestine and on blood pressure. *Anesthesiology* 6: 231-238, 1945.
22. Griffith, H. R. Curare in anesthesia. *J A M A* 127: 642-644, 1945.
23. Cullen, S. C. Use of curare for improvement of abdominal muscle relaxation during inhalation anesthesia: report on 131 cases. *Surgery* 14: 261-266, 1943.
24. Knight, R. T. Use of curare in anesthesia. *Minnesota Med* 27: 667-670, 1944.
25. Harroun, P., Beckert, F. E., and Hathaway, H. R. Curare and nitrous oxide anesthesia for lengthy operations. *Anesthesiology* 7: 24-28, 1946.
26. Gross, E. G., and Cullen, S. C. Effects of anesthetic agents on muscular contraction. *J Pharmacol & Exper Therap* 78: 358-365, 1943.
27. Brody, J. Use of curare in sodium pentothal nitrous oxide-oxygen anesthesia. *Anesthesiology* 6: 381-384, 1945.

EXPERIENCES WITH CURARE IN ANESTHESIA*

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THE use of curare in anesthesia has rapidly gained popularity within the past few years. Numerous papers, which agree on its usefulness, have been published since the initial study of Griffith.¹ These papers describe different methods of administration, advantages, limitations and possible disadvantages of the drug.²⁻⁹ There have also been publications of experimental studies that give further information.¹⁰⁻¹⁴

The main purposes of this paper are to consider the indications for curare and its comparison with other agents and to present experience with the use of curare (Intocostarin®) in 450 cases. The basis of discussion of the results in these cases lies in the segregation into four distinct groups in which

the special qualifications and the adaptation of curare are described. It will be noted that other uses of curare — for example, in bronchoscopy and cesarean section — are not considered.

The first group in which curare was administered comprised cases of elective abdominal surgery in which the choice of anesthesia presented no particular problem, for these cases were adaptable for any conventional type of anesthesia. With this group as a standard it was possible to evaluate the technique.

The method of administering curare with a light general anesthetic was that described by Cullen.² The agents used with curare were cyclopropane, Pentothal Sodium, nitrous oxide, ether and various combinations. The experiences and results corresponded with those of Cullen. Relaxation was found to be extremely satisfactory, in most cases, it was similar to the complete relaxation attained in spinal anesthesia. In quite a few cases, however, the onset of relaxation was delayed, additional doses and time being required. On the basis of this

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pressure, pulse and respirations showed little change throughout the operation. The patient left the operating table 20 minutes after the last dose of curare had been given. The breathing was approximately normal in depth, at a rate of 28 per minute. There was no obstruction, and the respiratory exchange was good. The patient's color was good. The blood pressure was 120/68, and the pulse 122.

The transportation from the operating room to the ward took about 12 minutes. On arrival in the ward, the patient was extremely cyanotic and did not breathe, although the pulse was satisfactory. Following artificial respiration for 30 minutes, she regained spontaneous breathing but remained comatose. With inhalation and shock therapy and administration of stimulants her condition improved. Six hours after operation, the blood pressure was 98/70, the pulse 124, and the respirations 36. The patient had a corneal reflex, and, on stimulation, moved her head. Two hours later, she went into shock. She expired 12 hours after operation.

It seems probable that the main cause of death in this case was that, in her serious general condition, the patient was subjected to severe hypoxia during the transportation. The asthma may have played a role in further aggravating the failing oxygenation. Unfortunately, the intern accompanying the patient on her way back to the ward did not recognize the respiratory obstruction, which in all probability was the cause of the hypoxia.

* * *

The choice of anesthesia for elective abdominal surgery in good-risk patients up to the introduction of curare was either spinal or deep general anesthesia, with or without the use of an intratracheal tube, other methods, such as intravenous and local anesthesia and varying combinations, were rarely employed. Curare with light general anesthesia now presents another choice. Our experience with the cases of the first group led to the conclusion that the order of choice of anesthesia is as follows: spinal anesthesia, light general anesthesia with curare and deep general anesthesia or other methods. Spinal anesthesia is still superior to any other methods for this type of surgery. Its simplicity, reliability and efficiency remain unsurpassed. If light general anesthesia with curare is compared to deep anesthesia or other techniques, it is our impression that the more favorable effect on the patient and the greater ease of administration make the former method preferable to the latter.

The problem of managing the cases in which the spinal anesthesia is wearing off and the intra-abdominal surgery is continuing has been simplified by the introduction of curare. In the cases in which a spinal anesthetic does not provide sufficient relaxation with the aid of a light general anesthetic, either curare must be added or the light general anesthesia must be deepened to obtain relaxation. The obvious advantages of the method employing curare are that the depression of the general condition of the patient is avoided, with a recovery period that is shorter and freer from complications, and that control of the problem is obtained with relative ease.

The use of curare in the anesthesia of poor-risk patients introduces a new variation of balanced anesthesia. By the use of light cyclopropane anes-

thesia with small doses of curare, this method employs the principle of balanced spinal anesthesia described by Wiggin.¹⁷ In both methods, two agents are administered in small amounts and are well tolerated by the handicapped patient. Since these agents act on different structures—the central nervous system and the neuromuscular junction and, in the balanced spinal anesthesia, the central nervous and peripheral nervous systems—their anesthetic effect is cumulative. Thus, satisfactory anesthesia can be accomplished by their balanced use with small doses that, if used alone, would be insufficient. The possible systemic effect of these low dosages is apparently not cumulative and seems to remain below the point where it would affect the general condition of the poor-risk patient to any appreciable extent. The administration of light cyclopropane anesthesia with curare or in balanced spinal anesthesia is similarly accompanied by the simultaneous administration of high percentages of oxygen and fluid therapy. This new variation of balanced anesthesia seems to be a valuable method for these types of patients.

The use of curare to facilitate intratracheal intubation adds another method to the various techniques of preparing patients for intubation. The advantage of this procedure is that it allows the anesthesiologist to use a light level of general anesthesia and to obtain complete relaxation in a relatively short time. The possible respiratory embarrassment following intubation is a disadvantage.

Postoperative complications that are respiratory in origin emphasize the importance of the physiologic control of respiration during the operation and the necessity of the same careful supervision of the patients who are under the effect of curare in the postoperative period.

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REFERENCES

1. Griffith, H. R. and Johnson, G. E. Use of curare in general anesthesia. *Anesthesiology* 3:418-420 1942.
2. Cullen, S. C. Clinical and laboratory observations on use of curare during inhalation anesthesia. *Anesthesiology* 5:166-173 1944.
3. Brody, J. Use of curare in sodium pentothal nitrous oxide-oxygen anesthesia. *Anesthesiology* 6:381-384 1945.
4. Cole, F. Use of curare in anesthesia: a review of 100 cases. *Anesthesiology* 6:48-56 1945.
5. Whitacre, R. J. and Fisher, A. J. Clinical observations on use of curare in anesthesia. *Anesthesiology* 6:124-130 1945. *Idem*. Use of curare in anesthesia. *Ohio State M. J.* 40:1155-1157 1944.
6. Waters, R. M. Nitrous oxide-oxygen and curare. *Anesthesiology* 5:618 1944.
7. Adams, R. C. Curare as aid to relaxation in anesthesia. *S. Clin. North America* 25:735-739 1945.
8. Griffith, H. R. Use of curare in anesthesia and for other clinical purposes. *Canad. M. A. J.* 50:144-147 1944.
9. Cullen, S. C. Curare in anesthesia. *Surgery* 18:45-47 1945.
10. Gross, E. G. and Cullen, S. C. Effects of anesthetic agents on muscular contraction. *J. Pharmacol. & Exper. Therap.* 78:358-365 1943.
11. Ruskin, A. Ewald, J. and Dechard, G. M. Jr. Electrocardiogram of curarized human patients. *Dis. Nerv. System* 4:335-341, 1943.
12. Gross, E. G. and Cullen, S. C. Action of curare on smooth muscle of small intestine and on blood pressure. *Anesthesiology* 6:231-238 1945.
13. Fegler, J. Action of curare on respiratory center. *J. Physiol.* 100:417-422 1942.
14. Cole, F. New lethal dose of curare with some observations on pathology produced by large doses. *Anesthesiology* 7:190-197 1946.
15. Schmidt, C. F. Recent developments in respiratory physiology related to anesthesia. *Anesthesiology* 6:113-123 1945.
16. Griffith, H. R. Physiological and clinical action of curare. *Anesth. & Analg.* 25:45-51 1946.
17. Wiggin, S. C. Balanced spinal anesthesia. *Anesth. & Analg.* 18:193-195 1939.

was provided throughout the operation. The curare was administered in doses of 20 to 50 mg every three to five minutes, until the surgeon reported satisfactory relaxation. The total dose required in some cases was less than 50 mg, whereas other cases required as much as 120 to 150 mg during the operating time of two or three hours. The resulting operating conditions were satisfactory.

Light cyclopropane anesthesia with properly administered curare did not seem to burden the handicapped circulation of these patients by adding to the present or impending shock. On the contrary, by the addition of fluid therapy and the tonic action of cyclopropane with high oxygen percentage, the general condition of most of the patients improved during the operation. The clinical course in the cases in which subtotal gastrectomy was performed on patients with uncontrollable gastric hemorrhage was as gratifying as that of a similar case reported by Whitacre.⁵ Although several patients in this group were moribund before the operation, there was no death during the operation or during the immediate postoperative period.

The fourth group comprised patients who required endotracheal anesthesia. Curare was given to facilitate the intubation by relaxing the jaw and throat musculature.

The following method of administration was found to be the most satisfactory. Cyclopropane or Pentothal anesthesia was induced, and curare was simultaneously administered in doses of 20 to 50 mg. The first dose was given at the time when anesthesia started, and further doses were given every three or four minutes. Within eight to ten minutes the patient was in the lower first or upper second plane of the third stage, relaxed and breathing quietly with sufficient depth. The intubation, which took place at that time, was easy and smooth in the majority of cases.

There were, however, respiratory disturbances of minor significance following the intubation in a certain number of cases. The regular rhythmic breathing sometimes stopped, and there was complete cessation of breathing, interrupted with occasional jerky inspirations. This respiratory embarrassment lasted in most cases for a few minutes, although there was one case in which it lasted for thirty-five minutes. In some cases, while controlled breathing was being administered during this period of respiratory embarrassment, the inflation of the lungs met with resistance, indicating that the patient was having a bronchial spasm. Whitacre⁵ and Griffith¹⁶ call attention to the fact that bronchial spasm occurring during curare administration is due to insufficient depth of the general anesthesia, in addition to the presence of a gross stimulus. The stimulus in these cases was the intubation and the tracheal tube lying in the trachea. In other cases the lungs could be readily inflated, indicating that the apnea was due to respiratory paralysis,

which developed during or immediately following the intubation. To avoid such respiratory disturbances, it seems necessary to stay within a narrow margin of proper depth of general anesthesia and of proper dosage and timing of curare.

The administration of curare for intubation in such a manner that the patient is deliberately put into apnea, the intubation taking place during apnea, has the disadvantages that during the intubation the controlled breathing—that is, the oxygenation of the patient—is interrupted and that it is difficult to re-establish spontaneous respiration with sufficient depth of the general anesthesia, both of which may be necessary in intrathoracic operations.

If ether is used as the main anesthetic for the ensuing operation, its administration, in the form of a slow addition to the cyclopropane or Pentothal, may be started before or after intubation. The amount of ether used in such cases need not exceed a third or a fourth of the amount that would be required if curare were not used. An hour and a half to two hours after the intubation is necessary before the ether requirement approximates the usual amount.

The recovery period in cases of all the groups was generally uneventful and brief, corresponding to the findings of others. Three cases, however, presented complications during recovery. Two of these showed postoperative respiratory depression. One patient, who had received cyclopropane and a small amount of ether with curare, recovered four hours after the operation. The other, who had received a spinal anesthetic followed by cyclopropane and curare, had a recovery period lasting seven hours. These patients were in shock, with depressed breathing and with depression of the reflexes during the postoperative interval. They recovered gradually and completely. Neither the surgery performed nor the anesthetic administered seemed to give sufficient reason in either case for this postoperative complication. It appeared reasonable to assume that hypoxia, which probably developed during the period of shallow breathing following the administration of curare, was an important cause. In these cases, which occurred at the beginning of the series, the anesthesiologist did not support the patient's spontaneous shallow breathing. The experiences with these cases in particular led to the conclusion that depressed respiration should be managed as described above.

In the following case postoperative depression was followed by a fatal outcome.

M. M., a 57-year-old woman with bronchial asthma, was operated on for intestinal obstruction of 4 days' duration. Her general condition before operation was fair. The operation included an extensive exploration, a lysis of adhesions and an ileocecostomy. A spinal anesthetic was administered and was supplemented with Pentothal and curare after 1 hour and 25 minutes. Curare was given in repeated doses totaling 100 mg. During the operation, 100 per cent oxygen was administered, and a transfusion was given. The blood

of other causes without recurrence the five-year cure rate is 89 per cent for patients without involvement of the lymph nodes, 34 per cent for those with lymph-node involvement and 50 per cent for the whole series. We are convinced that the complete radical operation should be done at the time of the first surgical approach to a cancer of the breast.

Three of the 6 patients on whom simple mastectomies were performed are without present evidence

nodes over 2.5 cm in diameter all or nearly all lymph nodes involved and signs suggesting a possible inflammatory type. We believe that wide removal of skin minimizes local recurrences, but unless one is too selective in choosing cases for operation a few recurrences are inevitable.

The extent of involvement of the axillary lymph nodes is of great prognostic significance, as shown by Warren and Tompkins⁶ in a study of cases from

TABLE 1 Results of Radical Mastectomy in 70 Cases at Westfield State Scraper and

TYPE OF CASE	PATIENTS WELL 5-8 YEARS AFTER OPERATION		POSTOPERATIVE DEATHS		PATIENTS ALIVE WITH CANCER		PATIENTS DEAD WITH CANCER		PATIENTS DYING OF OTHER CAUSES	
	NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE
No metastases to lymph nodes	16	64	1	4	1	4	4	16	7	12
Metastases to lymph nodes	14	51	2	7	7	26	7	7	0	0
Totals	30		3		8		11		7	
Averages		45		4		6		43		4

of cancer. We do not believe, however, that simple mastectomies should be done with the expectation of cure.

Table 2 presents the comparative results of a few previous studies. In the series at the Massachusetts General Hospital¹ and in our series all recurrences—even those after five years—and operative deaths are considered failures. Deaths from intercurrent disease are excluded. The figures in the Mayo Clinic⁴ series represent five-year survivals. The

the Massachusetts State Cancer Hospital at Pondville. When all the axillary nodes showed metastases, there were no cures in our series although one patient lived over five years before developing a recurrence.

We have not considered microscopical grading of sufficient value for routine use. Our pathologist, however, reviewed the slides with the following results. There were 4 cases of Grade I carcinoma with 75 per cent five-year cures, 31 cases of Grade II,

TABLE 2 Five-Year Clinical Cures following Radical Mastectomy

TYPE OF CASE	ALL WESTFIELD CASES		CASES WITH PRIMARY OPERATION AT WESTFIELD		WESTFIELD CASES WITH OPERATION ELSEWHERE		MASSACHUSETTS GENERAL HOSPITAL ¹		MAYO CLINIC ⁴		PRESBYTERIAN HOSPITAL ²		HARTFORD HOSPITAL ³	
	NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE
No metastases to lymph nodes	22	73	17	89	42	24	60	70	1634	74	237	61	154	69
Metastases to lymph nodes	45	31	41	74	61	16	114	31	2915	26	785	21	216	24
Totals	67		58		103†		174		4549		1022		370	
Averages		45		50		18		45		45		36 (40*)		42 (45*)

*Eliminating untreated patients and those dying of other causes.

†The status of the lymph nodes was unknown in 22 additional cases in this group.

figures at Presbyterian Hospital² represent the clinical cures divided by the number of operations. Ten, or 14 per cent, of the patients in whom radical mastectomies had been performed developed local recurrences, some of them after five years. Other published series have varied in this factor from Rodman's⁵ 2.2 per cent to Haagensen and Stout's⁷ 22.8 per cent. There were no recurrences of cancer in the axilla in our series. An analysis of our cases disclosed that in all but 2 in which neoplasm reappeared in the operative field there were features of questionable operability, such as axillary lymph

nodes with 48 per cent cures, and 24 cases of Grade III, with 37 per cent cures.

One hundred and twenty-five patients in whom mastectomies had been performed elsewhere were followed in our clinic. In a few, radical operations had been performed at the Massachusetts State Cancer Hospital in Pondville, and the patients had been transferred merely for routine examination. Most of them had been operated on in various local hospitals and had been referred to us for x-ray treatment.

CARCINOMA OF THE BREAST

A Review of the First Three Years' Experience in the Cancer Section of the Westfield State Sanatorium

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TWO hundred and fifty-eight patients with carcinoma of the breast were seen in the Cancer Section of the Westfield State Sanatorium in its first three years, 1938 through 1940. In 70 cases a radical operation was done in hope of cure. Simple mastectomies were performed in 7 cases, whereas 138 patients were referred after having been treated at other hospitals.

Thanks to an extremely efficient social-service department, all these patients have been followed. All except 4 of the surviving patients who were operated on are still being regularly examined at the clinic, and the others have been visited by one of the social workers.

Our routine procedure at the time of the first visit of a patient with suspected cancer of the breast consisted in x-ray films of the chest, as well as the upper ends of the humeri, the skull, the spine and the pelvis, including the upper ends of the femurs. Unsuspected metastases have been found in several cases that would otherwise have been deemed operable. Other contraindications that we have followed are fixed, matted lymph nodes in the axilla and definite inflammatory carcinoma. If there is any suspicion of involvement of the supraclavicular nodes, a biopsy is done first. In this series the patient's general condition has not been considered a contraindication to operation, although most of the simple mastectomies were done because of poor physical condition. There were deaths in 3 cases after radical operations, however, and 1 fatal case following a simple mastectomy—all in patients over seventy years of age and in poor physical condition. Johnson and Lombard¹ have shown that the operative mortality in cancer is directly proportional to age. Since then we have more carefully evaluated patients in the older age group and refer them for radiation treatment unless we believe that they have a life expectancy of at least five years. After this procedure had been adopted, there were no postoperative deaths.

The operations were performed by thirteen members of the visiting and resident staffs. Most operations began with a local excision of the tumor and a frozen section to confirm the diagnosis. A formalin-soaked sponge was placed in the cavity before suturing, and the wound was sealed with collodion and gauze. The usual incision was of the Rodman-

Greenough type. We believe, however, that the important feature is to make the incisions include an area of skin at least as wide as the breast and with the tumor at least 5 cm from the incision. After the pectoral muscles have been divided at their insertions, a meticulous dissection of the axilla is made, all areolar tissue being removed from the axillary vein. The upper rectus fascia is removed with the breast, muscles and axillary contents. Wide undercutting usually permits closure without grafting. The value of thorough, extensive dissection is clearly illustrated by the report of Haagensen and Stout,² who found no statistically significant difference in the results of various types of radical mastectomies. But the cure rate was in direct proportion to the duration of the operation. The rate for procedures lasting less than an hour was 28.6 per cent, whereas for each successive hour of operating time it was 35.3, 34.3, 43.7 and 56.3 per cent respectively.

Preoperative x-ray treatment was not used, but all patients with axillary metastases were given postoperative radiation. The usual dose was 7200 r. Four portals were employed, 1800 r being given to a 10-by-15-cm supraclavicular area, to a 10-by-10-cm axillary area, to a 10-by-15-cm posterior axillary area and to a 15-by-15-cm area on the anterior chest wall. The other factors were a constant potential of 200 kilovolts, a wave length of 0.16 angstrom, a distance of 50 cm, and a filter of 1 mm aluminum and 0.5 mm copper. Women who were still menstruating were offered ovarian radiation, which most of them accepted.

In the determination of results, operative deaths and patients alive with recurrence were classed as failures. Of the 70 patients who had radical operations 30, or 43 per cent, are living and well without evidence of cancer. Of the 45 cases with axillary metastases 14, or 31 per cent, are considered five-year cures. When no involvement of the axillary lymph nodes was found 16 of 25 patients, or 64 per cent, are living and well (Table 1). Three of the deaths, however, were from other causes without evidence of recurrence. With the elimination of these cases the cure rate is raised to 73 per cent. Nine of the 70 patients with radical operations had had either a simple mastectomy or local excision of a tumor before being referred to us. Of these only 3 cases are considered clinical cures. Five patients showed no evidence of axillary metastases. If these are eliminated, as well as those dying

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cancer, are factors indicating a poor prognosis. The percentage of axillary lymph nodes showing metastasis and the microscopical grade of the tumor are also of valuable prognostic significance. It is dangerous to rely on the clinical impression regarding the involvement of the nodes. In 11 cases the pathologist found metastases that were not diagnosed clinically, whereas in 3 the nodes were considered involved but no metastases were found.

This series does not permit any significant evaluation of x-ray treatment. The patients with involvement of the axillary lymph nodes gave us slightly better results than those in most of the published statistics, and all of them were given postoperative radiation. We do not believe, however, that the results can be attributed to the radiation. All except one of the patients who developed local recurrences had had x-ray treatment. We believe that the patients who received only palliative x-ray treatment were made much more comfortable and that there was some prolongation of life. We have recently omitted routine postoperative x-ray treatment of patients with axillary metastases.

SUMMARY

Two hundred and fifty-eight patients with cancer of the breast seen at the Cancer Section of the Westfield State Sanatorium over five years ago are reviewed. Fifty-nine, or 23 per cent, were considered five-year clinical cures. Thirty, or 43 per cent, of the 70 patients who had radical mastectomies at Westfield are alive without evidence of recurrence five to eight years following operation. Ten, or 14.5 per cent, of this group had local recurrences. There was no case of recurrence in the axilla. Twenty-two, or 18 per cent, of the group that we

followed who had had radical mastectomies elsewhere are apparently cured.

The observance of the operative criteria proposed by Haagensen and Stout would improve the figures of five-year survivals but would allow an occasional patient to receive only palliative treatment when there was a possibility of obtaining a cure. These criteria are of prognostic value.

The percentage of lymph-node involvement and the microscopical grade of the tumor are of aid in prognosis.

X-ray treatment is of great help in making the patient more comfortable.

The value of a complete radical operation at the time of the first surgical approach to cancer of the breast is illustrated by the fact that whereas our percentages of five-year clinical cure were 73 per cent with negative nodes, 31 per cent with axillary metastases and 45 per cent for the series, by the elimination of patients who had previous operations the corresponding percentages were 89, 35 and 50 per cent.

REFERENCES

- 1 Johnson A. S. and Lombard H. L. Estimation of operative risk in patients with cancer. *New Eng J Med* 224:759-762 1941.
- 2 Haagensen C. D., and Stout A. P. Carcinoma of breast: results of treatment. *Ann Surg* 116:801-815 1942.
- 3 Simmons C., Taylor G. W. and Welch C. E. Carcinoma of breast: end results. Massachusetts General Hospital 1930-1931 and 1932. *Surg., Gynec. & Obst.* 69:171-177 1939.
- 4 Harrington S. W. Results of radical mastectomy in 5026 cases of carcinoma of breast: various clinical and pathologic factors which influence prognosis. *Pennsylvania M J* 43:413-427 1940.
- 5 Rodman J. S. Skin removal in radical breast amputation. *Ann Surg* 118:694-705 1943.
- 6 Warren S. and Tompkins V. N. Significance of extent of axillary metastases in carcinoma of female breast. *Surg. Gynec. & Obst.* 76:327-350 1943.
- 7 Daland E. M. Untreated cancer of breast. *Surg. Gynec. & Obst.* 44:264-268 1927.
- 8 Haagensen C. D., and Stout A. P. Carcinoma of breast: criteria of operability. *Ann Surg* 118:1032-1051 1943.
- 9 Wells D. B. Unpublished data.

Twenty-two, or 18 per cent, of these 125 cases were considered five-year clinical cures. Of the 42 cases without evidence of axillary metastases 10, or 24 per cent, were apparently without recurrence, whereas of the 61 with extension to the lymph nodes only 10, or 16 per cent, were without evidence of carcinoma after five years. There were 22 cases in which there was no definite information concerning the status of the lymph nodes. Only 4, or 3 per cent, of the entire group developed local recurrences.

Forty-seven patients were considered inoperable when first seen and were treated by x-ray only. Of these, one is regarded as a five-year clinical cure and 2 have passed the five-year mark but have developed recurrences. The average length of life in this group was thirty-six months from the onset of the disease. These cases cannot be compared with Daland's⁷ series of untreated cases in which the average length of life was forty and a half months, because only the advanced cases were treated exclusively by x-ray therapy.

Haagensen and Stout⁸ have made a careful study of the criteria of inoperability and of factors of poor prognostic significance. The following are considered definite contraindications to operation: distant metastases, inflammatory type of carcinoma, supraclavicular metastases, edema of the arm, intercostal or parasternal nodules, satellite nodules in the skin over the breast, extensive edema of the skin over the breast and carcinoma developing during pregnancy or lactation. They obtained no cures in this group, which they call "categorically inoperable." Other factors of such poor prognostic significance that the presence of any two is regarded as a contraindication to operation include ulceration of the skin, limited edema of the skin (less than a third), fixation of the tumor to the chest wall, axillary lymph nodes measuring 2.5 cm or more in the transverse diameter and proved to contain metastases by biopsy and fixation of axillary lymph nodes to the skin or the deep structures of the axilla, with the nodes proved to contain metastases by biopsy.

Although we have always considered inflammatory carcinoma to be a contraindication to operation, there was 1 operative case that was apparently of the inflammatory type. This promptly recurred. Two patients had redness of the skin and slight local heat. Each had some other feature of questionable operability. One of these is living and well. In 1 patient the axillary lymph nodes over 2.5 cm in diameter with questionable fixation were found to be merely inflammatory, and there is no evidence of recurrence. The 12 other cases with various combinations of ulceration, limited edema, fixation to the chest wall, satellite skin nodules, axillary lymph nodes over 2.5 cm in diameter, questionable fixation of nodes, preoperative edema of the arm or redness of skin or local heat are all considered failures.

The other factors mentioned by Haagensen and Stout did not occur in this group.

A thorough statistical review of 570 cases of carcinoma of the breast with radical mastectomies in 350 has recently been made by Wells,⁹ of the Hartford Hospital. Two of the 3 cases in which cancer developed during pregnancy or lactation were classified as ten-year cures. In the group in which two factors of poor prognostic significance were considered a contraindication to operation there were a few scattered cures in both series except when either multiple tumors or skin edema was combined with other factors. In the group that would be classified as inoperable by Haagensen and Stout,⁸ Wells⁹ had 57 cases of which 8, or 14 per cent, were considered five-year clinical cures, and 7 apparently permanent cures. Harrington,⁴ of the Mayo Clinic, reported 99 operated cases of cancer of the breast developing during pregnancy or lactation, with axillary metastases in 84.8 per cent. In this group the five-year and ten-year survivals were 7.7 and 3.1 per cent, whereas in those without axillary metastases the figures were 57.1 and 38.5 per cent respectively.

DISCUSSION

Although this is too small a series to be statistically conclusive, we believe that it emphasizes certain important facts. One cannot repeat too often that a thorough radical operation will cure most cases of cancer of the breast if performed before there are axillary metastases. In our cases in which the lymph nodes were already involved 31 per cent of patients are alive without evidence of cancer. A total five-year salvage of 43 per cent in all our radical operations is encouraging. This figure could be improved slightly by more strict adherence to Haagensen and Stout's criteria. We believe, however, that every case in which there is a possibility of cure should have the benefit of operation. We accordingly operate on many poor-risk patients except those with an estimated life expectancy of less than five years. Enough good results have been obtained in patients developing cancer during pregnancy or lactation to justify the attempt. Unless large axillary lymph nodes are firmly fixed, operation might obtain a good result, and the case should certainly not be classified as inoperable without a biopsy of the nodes. When the finding of satellite nodules, multiple tumors or skin edema is combined with other unfavorable features, there is too slight a possibility of cure to warrant operation. We agree that distant or supraclavicular metastases, inflammatory carcinoma, preoperative edema of the arm, intercostal or parasternal nodules and extensive edema of the skin are contraindications to operation. The other features, such as redness, ulceration or limited edema of the skin, fixation of the tumor to the chest wall and large or adherent axillary lymph nodes showing

dilated lateral ventricles were visualized that were highly suggestive of hydrocephalus internus. Some air was also observed to be trapped in the region of the cisterna magna, which appeared much larger than normal. Briefly, the films were consistent with generalized cortical atrophy, hypoplasia or aplasia of the cerebellum and possibly, internal hydrocephalus.

Lumbar puncture was repeated on January 3, and analysis of the cerebrospinal fluid showed a total protein of 234 mg per 100 cc.

The temperature began to exhibit wide fluctuations on January 4 and 3 days later reached a maximum in excess of 105°F. Enemas, clyses, sponges and the ingestion of acetylsalicylic acid were followed by a reduction in temperature. The infant was having fourteen loose green stools a day by January 9 and was put on fluids and sulfadiazine. On January 11 the red-cell count was 2,560,000, and the white-cell count 6600, the temperature became more regular, and the diarrhea showed signs of abating. The intravenous administration of 10 cc. of whole blood, however, failed to effect an improvement in the red-cell count.

On January 14 the patient developed nuchal rigidity, convulsions, spastic movements of the extremities, opisthotonos and an elevated temperature, without, however, exhibiting bulging fontanelles. Cerebrospinal fluid obtained by lumbar puncture was clear, with a total protein of 85 mg per 100 cc, no leukocytes and a few crenated and noncrenated red cells, culture showed no growth after 72 hours. Symptomatic therapy resulted in significant improvement and the course was uneventful until February 10, when diarrhea again developed. A site of infection was not found, but routine therapy with fluids and sulfadiazine was again followed by improvement. The weight gain continued to be satisfactory. Fluctuations in temperature, never entirely absent again became marked, the temperature periodically dropping as low as 93°F.

Re-evaluation of the patient at 4 months of age showed paralysis of the right leg extending to and including both gluteal muscles and no alteration in the talipes equinovarus of the right foot. The left leg was better developed and had more substance, but it was far from normal. The pilonidal sinus was still clearly evident. The lesions on the skin of the left thigh were white, raised and slightly irregular. A severe torticollis to the right was present, and only by force could the head be maintained in normal position. The eyes exhibited continuous lateral nystagmoid movements. Ophthalmoscopic examination revealed bilateral optic atrophy and a peculiar darkish pigmentation of the retinas. On the whole, the patient appeared abnormally quiet and inactive.

A glucose-tolerance test done on April 17 showed the blood sugar to be 89 mg per 100 cc. fasting, 160 mg at 30 minutes, 129 mg at 1 hour, 125 mg at 2 hours and 127 mg at 3 hours, no urinary sugar was found during the test period.

Except for the sudden appearance and remission of spasticity, vomiting and bulging fontanelles on March 15 not due to meningitis, the course continued uneventful, and the patient was discharged on April 29 under the supervision of the Social Service Department.

Although a purely pathological diagnosis is not feasible in this case, it may prove interesting to list the defects that may justifiably be considered to have been present: talipes equinovarus, right, paralysis and muscular atrophy, right lower extremity, defective development, toes of right foot, cortical atrophy, hypoplasia or aplasia of cerebellum, internal hydrocephalus, bilateral optic atrophy, pilonidal sinus, torticollis to right, cicatricial (? post-varicella) lesions, skin of left lower extremity, undescended testicle, left, and insufficiency of anal and vesical sphincters.

In addition, certain defects of a preponderantly physiologic nature were noted, such as hyperirritability of the central nervous system, poorly functioning thermoregulatory ability and an apparent increased susceptibility to infection.

DISCUSSION

The case presented above is one in which a well authenticated episode of maternal varicella complicating the eighth week of pregnancy was followed by term delivery of an infant with extensive developmental defects. The maternal and paternal family

histories were devoid of congenitally malformed offspring. A three-year-old sibling of the patient was normal. Apparently, then, constitutional factors may be minimized as contributing to the etiology of the multiple defects, whereas the possibility is enhanced that the prenatal varicella was the responsible agent. As Conte, McCammon, and Christie³ point out, however, it is difficult to evaluate the significance of reported cases because it is not known how often virus infections occur without congenital malformations or how often malformations occur without virus infections—in other words, there are no controls for the reported cases. An effort was made to determine the frequency with which maternal gestational varicella was followed by offspring with such severe congenital defects, but in a review of the literature no similar reports could be discovered. At this writing, the case detailed above is apparently the first of its kind to appear in the literature, although we may be unacquainted with pertinent prior papers. In this connection, however, it may be interesting to quote, in toto, a case cited by Conte, McCammon and Christie³ together with their comment:

Case 7. J. M., a white boy, was born at term of a 23-year-old mother, who had chickenpox in the second week of her pregnancy. Delivery was normal. His immediate neonatal condition was good. His birth weight was 7 pounds (3,175 gm). There was no congenital anomaly found in this infant. The varicella occurred in the first month and was not followed by a congenital anomaly in the child. There have been no previous observations made concerning the relationship between this disease and congenital anomalies.

Failure of this infant to demonstrate defects does not necessarily negate or modify the possible propensities of maternal gestational varicella for the production of anomalies. In the first place, the disease was contracted in what was apparently the second week of pregnancy, however, since estimated dates of conception are notoriously inaccurate, it is possible that the mother did not actually become pregnant until after the disease had been experienced. Swan and Tostevin⁶ remark the absence of congenital defects following rubella that occurs just before pregnancy. Again, the third principle of Stockard⁷—cited below—may have been operative. A final explanation, which admittedly cannot be definitely excluded at present, is that maternal varicella bears only a coincidental and not an etiologic relation to subsequent infantile anomalies.

More or less incidentally in a paper concerned chiefly with the relation of maternal gestational rubella to congenital defects, Swan and Tostevin⁶ mention 2 cases of pregnancy complicated by varicella, in both of which the mothers contracted the disease in the seventh month. One of the infants born subsequently was normal, the other had a nevus of the scalp, and the x-ray findings were suggestive of a cardiac defect—an enlarged heart, a small aorta and configurations indicating right

MULTIPLE CONGENITAL DEFECTS FOLLOWING MATERNAL VARICELLA*

Report of a Case

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INVESTIGATION of the factors responsible for congenital malformations received tremendous impetus in 1941 with the classic report by Gregg,¹ of Australia, of a series of cases in which maternal rubella was followed by a variety of anomalies in the offspring, particularly such ocular defects as cataract. Previously, it had been generally accepted that malformations do not result from environmental factors that operate for the first time after fertilization.² Attention, therefore, had been directed chiefly at possible preconceptual causes. The studies of Gregg¹ and of numerous subsequent workers, however, emphasized the necessity of according careful consideration to environmental conditions obtaining after the fetus has become established.

The significance of this newly adopted approach to the problem of congenital malformations is already well recognized, and a voluminous literature has sprung up since the initial publication from Australia. Considered from the aspect of preventive pediatrics, therefore, the potentialities of continued work in this field are gratifying.

The maternal virus disease that thus far appears to be the most frequent offender is rubella. In 1945 Conte, McCammon and Christie³ collected 136 cases of congenital malformation with a definite history of maternal prenatal virus infection, in all but 2 of which rubella was the associated disease, a case of mumps and one of influenza constituting the exceptions.⁴ On the basis of analogy, however, the suspicion is growing that the incidence of congenital malformation following other maternal prenatal virus infections parallels that associated with rubella. This is suggested by Fox and Bortin,⁵ who recommend more extensive investigation of the possible relation of congenital malformations to any of the virus diseases that occur during gestation. In the following case maternal varicella occurring in the eighth week of pregnancy was followed by delivery of a child with extensive congenital defects.

CASE REPORT

A 6-hour-old infant (B F H 90816) was admitted to the hospital on October 27, 1945, because the attending physician had detected an anomaly of the right leg. The mother, a 23-year-old housewife, had had pertussis, rubella and asthma in childhood, at the age of 7 or 8 years she had been unable to bear weight on her legs and was presumed to have had

rickets at that time. So far as could be ascertained, there was no family history, either maternal or paternal, of congenital anomalies. The mother had contracted varicella in the 8th week of pregnancy, when she was "covered from head to foot" with lesions and had a temperature of 102°F for two weeks. The diagnosis of varicella was well established, since the case had apparently been a classic one. A 3-year-old female sibling of the patient had also had varicella synchronously with the mother. The course of the pregnancy had been normal except for an occasional whitish vaginal discharge that was more marked in the morning. The gestation proceeded to term, delivery being by vertex and spontaneous.

Physical examination revealed a poorly developed, normally nourished infant. The skin was pinkish and normal except for several well defined reddish pigmented areas, 3 to 5 mm in diameter, on the medial aspect of the left thigh and leg. The head was round and regular. The eyes showed only questionable reaction to light. The scleras and conjunctivas were clear. There was no nasal discharge. Otoloscopic examination disclosed normal tympanic membranes bilaterally. The oral cavity and oropharynx were normal. There was no nuchal rigidity or cervical lymphadenopathy. The lungs were resonant and clear. The heart was not enlarged to percussion, and no abnormality of rate, rhythm or sounds was detected. The abdomen was soft. The liver was palpated three finger-breadths below the right costal margin. The spleen could not be felt. No costovertebral swelling or other abdominal masses were discovered. Grossly the external genitalia appeared normally developed except for an undescended left testicle, but urine constantly dribbled throughout the examination. The anal sphincter, which was at the level of the buttocks, was relaxed and widely patent, presenting a continuous discharge of fecal material. The extremities were normal except for the right lower leg, which was thin and underdeveloped in comparison with its mate, and a right talipes equinovarus, the toes of the right foot were underdeveloped, the terminal phalanges being represented only by small horny pegs, and the great toe was in abnormal apposition. The muscular atrophy of the right leg extended to the gluteal region. The deep tendon reflexes were physiologic except for an absent knee jerk on the right and an unelicitable Achilles reflex on the right. In the lumbar region there was a longitudinal depression, 3 cm in length and 0.5 cm in depth, that was free of discharge. Routine urinalysis and blood counts on admission were not remarkable.

X-ray studies on October 29 revealed no evidence of increased intracranial pressure or of any abnormality of the vertebral column. A chest plate was normal. Films of the right leg and foot were reported as follows:

The right lower extremity is markedly underdeveloped. The bone is retarded in development and the soft tissues have an abnormal appearance. The foot is particularly deformed, the 4th and 5th toes having only a basal phalanx and no middle or end phalanges. The size of the individual bone is but a fraction of that of a normal one. This is obviously a congenital anomaly of a developmental character.

The right leg showed no improvement and apparently was not growing. Actively, it could not be fully extended at the knee, and even passively could not be fully flexed at the hip. Measurement on December 10 revealed it to be 2 cm shorter than the left.

After two previous attempts at lumbar puncture had resulted in bloody taps, a third on December 19 was satisfactory, analysis was essentially normal except for a total protein of 160 mg per 100 cc. Bilateral subdural taps were also done on this date and disclosed a large amount of clear fluid, also with a high protein content (117 mg per 100 cc).

On January 2, 1946, a pneumoencephalogram was performed, 30 cc of air being injected over a period of 2 hours after the withdrawal of 35 cc of cerebrospinal fluid. Large

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11 Senator Cited by Schamberg J F Chickenpox In *Nelson Encyclopedia of Living Medicine* Vol. 1 New York Thomas Nelson & Son 1926. Pp 529-544

12 Irenskaya E A. Chickenpox in premature children *J russk medk rev* 9:504-508 1930

13 Troitskaya A Y. Course of chickenpox in nurslings. *J russk medk rev* 12:91-95 1932.

14 Smits J W Herpes zoster en varicellen *Nederl tijdschr - geneesk* 76:1703 1932.

15 Casprave, A K., and Samuel J Case of congenital chicken-pox *Melaysia M J* 9:68 1934

16 Henderson W B Chickenpox in eight day-old infant *J Pedic.* 4:668-670 1934

17 Baron F Un cas de varicelle mortelle chez le nouveau ne par contagion materielle *Bull. Soc d'obst et de gynec* 24:67 1935

1 Mitchell, G A. Cited by Shuman 20

19 Campbell E P. Chickenpox in twelve day old infant *Am J Dis Child* 57:1408-1410 1939

20 Shuman H H Varicella in newborn *Am J Dis Child* 58:564-570 1939

21 Oppenheimer E H Congenital chickenpox with disseminated visceral lesions *Bull Johns Hopkins Hosp* 74:240-250 1944

22 Lynch F W Dermatologic conditions of fetus with particular reference to varicella and vaccinia *Arch Derm & Syph* 26:997-1019 1932.

23 Watson W Some accounts of fetus in utero being differently affected by small pox *Phil Tr (London)* 46:693 1749

24 Warner, E Acute an encephalomyelitis complicating pregnancy *Acta Med Scandinavica* 123:207-218 1945

25 Aycock W L., and Ingalls T H Maternal disease as principle in epidemiology of congenital anomalies *Am J Hyg* 212:66-79 1946

MEDICAL PROGRESS

EFFECTS OF PROTEIN DEFICIENCY ON THE PREGNANT WOMAN AND FETUS AND ON THE INFANT AND CHILD (Concluded)*

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PROTEIN DURING INFANCY AND CHILDHOOD

Requirements

The primary function of protein in the diet is to provide the amino acids that are essential for the synthesis of tissue proteins characteristic of the species. In normal adults, new tissues are required only for replacement or maintenance. Disease and trauma may cause a rapid loss of nitrogen and greatly increase the need for protein at any age. In infants and children three additional factors must be considered. The young person differs from the adult in that he is immature, he is small, and he is growing. For the most part, infants and children utilize protein well, but normal infants and especially premature infants need protein in a physical form that their digestive tracts can readily assimilate. Levine³⁵ in a recent review, cited an example of the influence of immaturity on protein needs. The premature infant has difficulty digesting and absorbing fat and tends preferentially to use protein, as well as carbohydrate, to provide energy, thus increasing protein requirements. Although immaturity undoubtedly increases the margin that must be provided over and above actual tissue requirements, this characteristic of early life is not a major one in determining total protein needs. Body size influences to some degree the amount of protein that must be provided when requirements are considered on the basis of unit of body mass. The relation of total maintenance or basal needs to body size is not a direct one of straight-line progression, and hence the basal needs are not the

same per kilogram of body weight irrespective of size or age. This is apparently due to a relation between the basal caloric and protein requirements. It is well known that the smaller the animal, the higher the energy requirement on the basis of body weight. This need is more constant when based on a unit of surface area, which is relatively greater, the smaller the body mass. Hegsted³⁶ has pointed out that the protein requirement for maintenance is much more closely correlated with basal energy requirement than with body size. This is understandable since a high basal metabolic rate is associated with a high catabolism, and more materials are therefore required for anabolism. Total protein needs per kilogram of body weight are much higher in infancy than in childhood and somewhat higher in childhood than in adolescence, part of this difference, although as yet an undetermined one, is undoubtedly due to the relation of maintenance need to body size. The influence of growth on protein requirements in early life is the principal effect with which this discussion is concerned. Levine³⁵ points out that in infancy and childhood both the quality and the quantity of dietary protein must be adequate to cover growth requirements as well as maintenance needs, under which he includes the allowance for fecal loss. This loss averages between 10 and 15 per cent of the total protein at all ages but varies with the type and amount of protein food consumed and with the functioning of the digestive system. He emphasizes the fact that protein requirements are greatly influenced by the adequacy of the caloric intake.

Several studies on animals have shown that normal growth of the young depends on the provision of suitable proteins and that quantitatively equal amounts of different proteins result in different rates of growth depending on the biologic value of the

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This review was prepared for and presented in part at A Symposium on "Protein" at the celebration of the one hundredth anniversary of the University of Buffalo, September 27, 1946.
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ventricular preponderance. In both cases the disease occurred well beyond the period (first trimester) when congenital defects are most to be feared, and in the significant case the defects were neither severe nor extensive.

Carefully to be distinguished from congenital anomalies following maternal varicella (teratogenic varicella) is congenital varicella, in which the pathogenesis of the disease in utero closely parallels the course it pursues in its better known guise as an almost inevitable but relatively benign childhood exanthem. There have been numerous references to the occurrence of varicella in the newborn,⁸⁻²¹ some better substantiated than others, in these cases the mothers contracted the disease near term and presumably transmitted the virus transplacentally, the child either being born with a fully developed vesicular eruption or developing it so soon after birth that sources of infection other than intrauterine could be discounted.

To cause severe developmental defects varicella or other virus disease must apparently occur in the first trimester of pregnancy. Goodpasture believes that this susceptibility during early pregnancy may be due to the fact that young and relatively undifferentiated cells are a more propitious medium than mature cells.

In this connection, three experimental conclusions of Stockard⁷ cited by Swan and Tostevin⁶ are presented as being particularly applicable.

The type of abnormality is determined by the particular developmental "moment" at which the noxa acts. At different periods in the development of the ovum, certain primordia are undergoing rapid proliferation, and may be thought of as developing at a rate entirely in excess of the general developmental rate of the embryo. At such periods these primordia are peculiarly susceptible to unfavourable influences, while only slight or no ill effects may be suffered by the embryo as a whole.

The earlier the arrest the more numerous will be the types of defect found, and the later the arrest the more limited the variety of deformities, since there are fewer organs to be affected during their rapidly proliferating primary stages.

If development is arrested or retarded at a stage when no unusually rapid changes are taking place, a comparatively quiescent moment during which all parts are developing, but during which no particular or important part is proliferating at an excessively high rate, the embryo may escape injury.

Regarding the last conclusion of Stockard, Swan and Tostevin state "If such 'moments of indifference,' as Stockard calls them, occurred in the earlier months of pregnancy, they would serve to account for the (so far) rare cases in which mothers have contracted rubella during these months and yet have given birth to apparently normal infants."

Perhaps the first reference to congenital anomalies following maternal virus disease is the rather esoteric observation attributed by Lynch²² to Watson,²³ who, in a paper published in 1749, stated that the fetus "was liable to be infected [with variola] at a very different time and in a very different manner from the mother." The potentially teratogenic aspects

of maternal rubella are receiving increasing emphasis and are well known. Congenital anomalies have been reported following mumps,⁴ herpes zoster,⁵ rubeola⁶ and influenza.⁴ Conte, McCammon and Christie,³ after reviewing the literature, could find no reference to congenital malformation subsequent to maternal varicella, although the case reported above and the most recent survey by Swan and Tostevin⁶ indicate that such an occurrence is possible. Waaler²⁴ has discussed 8 cases of acute anterior poliomyelitis in pregnant women between eighteen and thirty-eight years of age, without the occurrence of fetal malformations. Nevertheless, in a review article concerned primarily with maternal rubella, Aycock and Ingalls²⁵ incidentally mention recent observations relative to poliomyelitis complicating gestation, and conclude that the risk to the fetus in maternal poliomyelitis is, as in German measles, high if the disease occurs in the first three months of pregnancy and less in later months. It is not clear, however, to what extent the hazard to the fetus is the result of paralysis in the mother. Conte, McCammon, and Christie³ have tentatively exonerated epidemic encephalitis, although not denying the possibility that it, too, may act as a teratogen.

Although not a virus disease, scarlet fever concurrent with pregnancy has occasionally been followed by developmental defects, such as congenital obliteration of the bile ducts in the case reported by Swan and Tostevin.⁶

SUMMARY

A case of multiple congenital defects following maternal varicella is reported. Present opinion on the pathogenesis of anomalies associated with maternal prenatal virus infection is reviewed. The possible teratogenic propensities of maternal virus diseases occurring early in pregnancy are emphasized.

REFERENCES

1. Gregg, N. M. Congenital cataract following German measles in mother. *Tr. Ophth. Soc. Australia* 3:35-46, 1942.
2. Murphy, D. P. *Congenital Malformations: A study of parental characteristics with special reference to the reproductive process*. 98 pp. Philadelphia: University of Pennsylvania Press, 1940. P. 97.
3. Conte, W. R., McCammon, C. S., and Christie, A. Congenital defects following maternal rubella. *Am. J. Dis. Child* 70:301-306, 1945.
4. Swan, C., Tostevin, A. L., Moore, B., Mayo, H., and Barham, Black, G. H. Congenital defects in infants following infectious diseases during pregnancy, with special reference to relationship between German measles and cataract, deaf-mutism, heart disease and microcephaly, and to period of pregnancy in which occurrence of rubella is followed by congenital abnormalities. *M. J. Australia* 2:101-110, 1943.
5. Fox, M. J., and Bortin, M. M. Rubella in pregnancy causing malformations in newborn. *J. A. M. A.* 130:568, 1946.
6. Swan, C., and Tostevin, A. L. Congenital abnormalities in infants following infectious diseases during pregnancy with special reference to rubella: third series of cases. *M. J. Australia* 1:645-659, 1946.
7. Stockard, C. R. Developmental rate and structural expression: experimental study of twins, "double monsters" and single deformities and interaction among embryonic organs during their origin and development. *Am. J. Anat.* 28:115-192, 1921.
8. Hubbard, T. W. Varicella occurring in infant twenty four hours after birth. *Brit. M. J.* 1:822, 1878.
9. Grindon, J. Apparent case of varicella in utero. *J. Cutan. Dis.* 19:237, 1901.
10. Priddy, F. C. Chicken pox during intrauterine life. *Brit. M. J.* 1:1054-1913.

kg in infancy may lead to negative nitrogen balances, levels above those recommended are wasteful since there are no body depots for reserve protein, absorbed amino acids in excess of the needs for growth and maintenance entering interchangeably with fat and carbohydrate into the energy exchange. With further deceleration in the growth curve with increasing age beyond infancy, lower levels of dietary protein per unit of body weight are required for nitrogen retention and protein deposition. The bulk of available evidence indicates that these recommendations [National Research Council allowances] are compatible with normal qualitative and quantitative nutrition as judged by the various means available.

It is generally agreed that if the appetite is normal, approximately 11 to 15 per cent of the calories of the diet should be provided by suitable protein foods at all ages, but a higher percentage may be required under special circumstances. Leitch and Duckworth,²⁸ who have reviewed this subject thoroughly, recommended allowances that are slightly higher at certain ages but in general are in substantial agreement with those of the Food and Nutrition Board. Youmans²⁹ makes similar recommendations.

Estimates of the actual amount of protein required by the infant and child at successive ages to provide for optimum growth tend to overlook several important considerations. Protein will be used first to meet the energy need, if this is not fully met from other sources. If the caloric intake is only moderately below the energy need and if reserve sources of calories have been exhausted, the drain on the protein intake for this purpose may be relatively great. Protein will next be used primarily for repair or maintenance, although some growth will undoubtedly take place at the expense of full maintenance and possibly also through the sacrifice of protein-rich body tissues. Only after these needs have been met will protein provide fully for the enlargement of such tissues as muscle. The points that should be stressed, therefore, in the protein requirements of children are that protein intake cannot be considered adequate unless caloric requirement is met, and that the first and most frequent effect of protein deficit is the limitation of growth. The effect of inadequate protein on growth is not easily recognized, and if correction of diet is not made until faulty growth is obvious or until other signs of deficiency are manifest, the child's progress often will have been considerably interfered with. Since it is not known how much constitutes adequacy for any given child at a particular time, a liberal margin of safety must be provided in the amount and quality of protein foods offered, together with an adequate caloric intake, and an otherwise well balanced diet, so that periods of interference with growth due to lack of protein can be avoided.

Youmans²⁹ has emphasized the importance of acute febrile illnesses as precipitating factors in manifest deficiency states. Infection increases caloric requirements, causes rapid catabolism with nitrogen loss and interferes with normal consumption and utilization of calories and protein, and children are subject to more such illnesses than adults.

Furthermore, the emotional disturbances often affecting both mother and child as a result of the latter's illness, often have profound effects on the child's eating habits and attitudes toward food and hence on food consumption. Youmans's contention applies with special force to childhood when he states that protein requirements are greatly increased by most illnesses and that failure to meet these increased needs by careful dietary planning in illness

TABLE 2 *Recommended Daily Allowances for Protein Expanded for the Growing Period*

Subjects	Age	PROTEIN PER KILOGRAM OF BODY WEIGHT
		gm
Premature infants	1 week to 1 month	6.0-4.4
Premature infants	1 to 3 months	4.4-3.3
Full-term infants	2 days to 3 months	4.4-3.3
All infants	4 months to 1 year	4.0-3.0
Toddlers	1 through 3 years	4.2-2.9
Preschool children	4 through 6 years	3.3-2.5
School children	7 through 9 years	2.6-2.1
School children	10 through 12 years	2.2-1.8
Youths female	13 through 15 years	1.8-1.5
Youths male	13 through 15 years	2.0-1.7
Youths female	16 through 20 years	1.6-1.4
Youths male	16 through 20 years	2.1-1.7

leads to a major number of protein deficiency states. It is difficult and often impossible to maintain nitrogen equilibrium throughout the course of many illnesses, and it is therefore of practical value to provide for storage of nitrogen during convalescence to an amount sufficient to replace damaged tissues and to afford the accelerated growth that usually follows periods of interrupted growth.

Effects of Protein Deficiency

It must be pointed out again that protein is rarely, if ever, the sole nutrient that is inadequate in a diet over any long period. The amounts of other essentials present have much to do with the effects of the protein level itself, and growth is known to be interfered with when various dietary essentials are sufficiently restricted. Except in animal experiments, one can rarely assume that poor growth has resulted solely or even primarily from a quantitative inadequacy of protein. There is a great deal of evidence, however, that low protein usually associated with low calories and continued over long periods is a frequent cause of poor growth in childhood. This evidence is derived in part from animal experimentation, in part from studies of the growth of children in tribal or national groups having different dietary habits, in small part from controlled studies of dietary supplements and restrictions, in part from combined dietary and growth studies of groups of children over long periods and more recently from studies of children subjected to inadequate diets as a result of war restrictions. This evidence is still far from complete, but a characteristic picture of the chronically underfed child, particularly regarding calories and protein, is beginning to emerge from it. Space does not permit a thorough review of these

protein A great body of evidence has been obtained in experience with infant and child feeding that testifies particularly to the unique value of milk proteins but also to the better growth attained on diets liberally provided with milk and other foods from animal sources. These furnish the essential amino acids in suitable proportions and liberal amounts. Nevertheless, Levine concludes, on the basis of evidence from studies on dogs, infants and adults, that positive nitrogen balances of similar magnitude result from equivalent intakes of protein, irrespective of the source of the dietary nitrogen if the protein offered provides all the essential amino acids in adequate amounts.

The quantitative requirements for protein at various ages prior to maturity are increased by an amount necessary to provide for the construction of new tissues laid down in the process of growth. One may arrive at an estimate of the protein requirements for growth in a variety of ways. Nitrogen balance studies on normal subjects, if conducted for sufficient periods, are indicative of the amounts of nitrogen being used for growth. One may also measure the amount of growth and from it estimate the amount of protein required to provide such a gain, but this involves a knowledge of the composition of growth. Since muscle tissue requires the highest deposition of nitrogen and since urinary creatinine excretion is a measure of the gain in muscle tissue, determinations of urinary creatinine excretion are useful in this connection. Clinical studies of growth under known dietary intakes are also useful but must be conducted over long periods and with precise methods both of dietary analyses and of measurements of growth. They throw light on the actual levels of habitual protein intake on which various levels of growth progress may be attained.

The amount of protein necessary to build the new tissues added with growth in any year is a relatively small proportion of the total protein needs when estimated on a daily-intake basis. This assumes that the protein is provided regularly in an otherwise adequate diet so that it is always available for growth. Talbot²⁷ has recently discussed the theoretical basis for this need and has called attention to the remarkably small daily positive nitrogen balance required to yield a significant growth of protoplasm in the course of a year.

Levine²⁸ states that, during infancy, the absolute retentions of dietary protein at equivalent and adequate intakes decline from 0.30 gm of nitrogen per kilogram of body weight daily in the premature infant to 0.15 gm at five months or older. As pointed out above, recommendations for protein allowances are usually expressed in terms of unit of body mass, — either kilograms or pounds of body weight, — but on this basis the need is influenced to some extent by size and consequently by age. It must not be assumed, therefore, that the difference

between the amount recommended on this basis for an infant and that for an adult is entirely due to the rapid growth of the former.

Estimates of protein needs based on theoretical considerations, animal experiments and studies of nitrogen balance, growth and diets in children lead to conflicting conclusions. They have thus far failed to give a clear picture of what the protein requirements are at succeeding ages for optimum growth and health. This is understandable for various reasons. In the first place, it is not known what constitutes optimum growth at any age or for any person. Furthermore, growth in the human being is a slow process, extending over two decades, and children cannot be kept on strictly controlled or known intakes over sufficiently long periods to allow accurate appraisal of growth. Gain in weight is not determined solely by growth, and gain in body length is not a true index of the amount of new tissues laid down.

Human growth progresses continuously from the embryonic period to full physical maturity, but by no means at the same rate at all periods or in equal proportions in different tissues. The protein required for the construction of some tissues is greater than that for others, muscle tissue creating the heaviest demand, and the new tissue components of a young person cannot be analyzed. There are two major cycles of over-all growth separated by a long interval of considerably slower growth. The rapid phase of early infant growth is accompanied by relatively large accumulations of fat in the subcutaneous tissues. The second phase of rapid growth is accompanied by a greater proportionate increase in muscle tissue. Although these changes with time are characteristic of human growth and persons differ only in their magnitudes and their rates of progress, individual differences in all these aspects are so great that variations in protein requirements must be considerable.

The recommendations of the Food and Nutrition Board⁹ may be considered to be as satisfactory guides to protein allowances for infants and children as are available at the present time. They must be recognized as applying only to average normal children within the broad age groups specified. Levine²⁸ has expanded these recommendations to deal more adequately with the subdivisions of the age groups with which they deal. His revised allowances are given in abbreviated form in Table 2. According to these recommendations, the full-term infant under one year of age should be provided a diminishing amount of protein varying from 4.4 to 3.0 gm per kilogram of body weight. Levine makes the following statement:

Analysis of available data for infants under one year establishes that these recommended daily allowances of protein are compatible with a normal rate of total weight gain and a ratio of nitrogen retained to total increment of gain which approximates the rising nitrogen content of the body. Protein intakes below 2.2 gm per

I spent some time during World War II attempting to collect evidence on these effects in studies of children in France, where, as elsewhere, a primary difficulty was lack of precise prewar standards with which to compare war and postwar children. Certain differences found in 1941 between French and American children⁴⁷ may well have resulted from this type of dietary, but it could not be said at the time that they were not national characteristics. After following a small group of the same children in Marseilles over a period of two or three years, Kuhlmann⁴⁸ found that as a group they failed to progress in weight and height to the amount expected for age. Although the numbers successfully followed were too small to give these results convincing significance, in approximately half the children studied growth was moderately but definitely retarded on the basis of normal expectancy and the average increment was approximately two thirds of expectancy.

Osseous development cannot be measured with sufficient precision to determine whether, in a given year or two, a group of children have fallen behind to a measurable degree, but it is of interest that in children studied in France in 1942 osseous development was, on an age basis, retarded in comparison with American standards to approximately the same relative extent as body size.⁴⁹

Another striking characteristic of the children in France and other countries suffering from war restrictions has been their lassitude and inactivity. This physical inactivity tends to spare calories and may conserve protein for structural purposes and appears to be another manifestation of natural adaptation. Diminished activity in childhood causes failure of normal muscle growth, complete inactivity leading to rapid muscle atrophy. It may be said with reasonable certainty that one of the major characteristics of chronic undernutrition in childhood is poor muscular development, and this has been one of the most striking features of the children seen in war-devastated or famine countries. This poor growth of muscle may be attributed to the lack of sufficient protein in the presence of inadequate calories or to lack of activity or, as seems likeliest, to a combination of these.

Keys,⁵⁰ in controlled experiments on conscientious objectors during the recent war, provided diets typical of those in the countries severely affected by the war. He found that most of the weight loss occurring during semi-starvation was due to the loss of muscle tissue. Other striking physical effects were progressive weakness and fatigue. In examining children in France I was impressed with the number who had reasonable amounts of subcutaneous tissue and hence appeared superficially to be well nourished and yet had extremely small and flabby muscles. This suggests that with loss of weight there is some initial loss of subcutaneous fat, but that after this has progressed to a certain but variable degree, further loss is primarily in muscle.

The children with poorly developed muscles were frequently found also to have rather spindly bones, and both linear growth of bones and osseous development appeared to be retarded. Owing to a lack of suitable prewar norms for comparison, however, this cannot definitely be stated to be a result of war. The question of an associated calcium factor enters into the picture. Protein and calcium are both liberally used in the construction of new bone. McCance⁵¹ has shown that calcium absorption is far more satisfactory when a high-protein diet is taken than when protein intake is low. Although the children in France received little milk and rarely any vitamin D supplement, clear evidence of rickets or poor calcium deposition in the skeleton was rarely seen after infancy, but the bones of these children frequently showed lines of interrupted growth. It may be that the poor bone growth observed in France was in part due to unsatisfactory amounts of vitamin D and calcium. It is probable, however, that it was also due to some extent to lack of protein, aggravated by the inadequate provision of calories.

Each of these studies may be considered a piece in a picture puzzle that is as yet far from complete. The general outline that is beginning to emerge, however, reveals that poor growth and development — particularly faulty muscle development and general lack of physical fitness — are frequent consequences of chronic low-calorie, low-protein nutrition in childhood.

I am greatly indebted to Mrs Bertha S. Burke for assistance in the preparation of this review.

REFERENCES

- 35 Levine S. Z. Protein nutrition in pediatrics. *J. A. M. A.* 128:283-287, 1945.
- 36 Hegsted D. M. Minimum protein requirements of normal adults. Lecture given in Symposium on Body Protein, University of Buffalo, September 1946. (To be published in University Centenary volume.)
- 37 Talbot, N. B., Sobel E. H., Burke B. S., Lindemann E. and Kaufman S. B. Dwarfism in healthy children: its possible relation to emotional nutritional and endocrine disturbances. *New Eng. J. Med.* (in press).
- 38 Leitch I. and Duckworth J. Determination of protein requirements of man. *Nutrition Abstr. & Rev.* 7:257-267, 1937.
- 39 Youmans J. B. *Nutritional Deficiencies: Diagnosis and treatment*. Second edition. 389 pp. Philadelphia: J. B. Lippincott Co. 1943.
- 40 Idem. Nutrition and war. *New Eng. J. Med.* 234:773-783, 1946.
- 41 Mitchell H. H. Adaptation to undernutrition. *J. Am. Diet. A.* 20:511-515, 1944.
- 42 McCarrison, R. Faulty food in relation to gastro-intestinal disorder. *J. A. M. A.* 78:1-8, 1922.
- 43 Idem. Problems of nutrition in India. *Nutrition Abstr. & Rev.* 2:18-19, 1932.
- 44 Mullick D. N. Investigations into Indian diets. I. Their effect on health and well being of three generations of rats. *Ann. Biochem. & Exper. Med.* 2:25-32, 1942.
- 45 Kruse, H. D., Betsey O. A., Jolliffe N., McLester J. S., Tisdall F. F., Wilder R. M., and Sydenstricker V. P. W. Principles underlying studies of nutrition pertaining to influence of supplements on growth, physical fitness and health with comprehensive bibliography of studies report by Committee on Diagnosis and Pathology of Nutritional Deficiencies. National Research Council. *Arch. Int. Med.* 74:258-279, 1944.
- 46 Main H. C. *Diets for Boys during the School Age*. 81 pp. Medical Research Council, Special Report Series No. 105. London: His Majesty's Stationery Office, 1926.
- 47 Stuart, H. C., and Kuhlmann, D. Studies of physical characteristics of children in Marseilles, France, in 1941. *J. Pediatr.* 20:424-453, 1942.
- 48 Kuhlmann, D. Personal communication.
- 49 Stuart H. C. Studies of nutritional state of children in unoccupied France in fall of 1942. preliminary report. *J. Pediatr.* 25:257-264, 1944.
- 50 Keys A. Human starvation and its consequences. *J. Am. Diet. A.* 22:582-587, 1946.
- 51 McCance, R. A., Widdowson E. M. and Lehmann H. Effect of protein intake on absorption of calcium and magnesium. *Biochem. J.* 36:686-691, 1942.

studies, but examples of each are cited, nor does it permit a discussion of the possible mechanisms involved in this slowing of growth when structural food substances are inadequate. The growth impulse is apparently so strong that children continue to grow in height and other skeletal dimensions while losing both fat and muscle. Various adaptations, however, sooner or later appear, and these have been more fully considered by Mitchell.⁴¹ Possibly, in the presence of undernutrition, the anterior portion of the pituitary body reduces its excretion of the growth hormone and thus lessens the need for protein by slowing the speed of growth. Other glands may then be affected, and osseous development and the genital changes associated with pubescence may be delayed. There is some evidence that these results actually do occur.

A number of classic studies in the literature show the effect of differences in dietary habits of different tribes on growth and health. The predominant differences in the diets of these physically different tribes were in the quantities of milk, meat and other animal foods consumed. Hence, the major, if not the principal, variants in them would be in the quality and quantity of the protein provided. The studies of Orr and Gilks¹⁵ referred to above offer a striking example. Two South African tribes living side by side under the same climate and with the same agricultural possibilities were chosen for study because they differed strikingly in size and vigor. The larger and more vigorous was a pastoral tribe and lived mainly on milk, meat and freshly drawn blood, whereas the smaller and less vigorous subsisted for the most part on cereals, roots and legumes. The children of the latter tribe were not only smaller than those of the former but were also much more subject to skeletal and dental defects and generally more poorly developed.

The studies of McCarrison⁴² on three tribes in India dealt with one tribe characterized by magnificent physique, unusual fertility and long life, and with two contrasting tribes in these respects. The superior tribe customarily took a simple diet of natural foodstuffs high in all the dietary essentials, the other tribes taking diets low in many of the essentials and obtained largely from plant sources. McCarrison's⁴³ findings on animals fed the same diets were even more striking. It is interesting that Mullick⁴⁴ recently repeated in India McCarrison's classic experiment on rats, with essentially the same results.

The well recognized fact that children of foreign nationals, such as the Japanese, born and brought up in this country are larger than their cousins who continue to live in their country of origin is further evidence along this line, in view of the associated differences in their diets under the changed circumstances.

The many studies of this type are in general agreement that, although heredity plays an important part, other influences are operative in determining

racial and national differences in physique and that diet probably plays a definite part. The principal dietary difference as related to growth and development in childhood seems to be in the consumption of milk and other animal foods, and hence in the quality and quantity of protein. The evidence is quite striking that this characteristic of diet is a major factor in determining the degree of muscular development and the general level of physical robustness, energy and health of a people.

The literature dealing with diet supplements in relation to growth and health during childhood appears to be contradictory and confusing. Kruse⁴⁵ has considered the factors involved that make this understandable and has presented a comprehensive bibliography. Obviously, when the diets of a group of children are adequate to provide for all needs, benefits will not be demonstrable from supplements, and the effect obtained in a given case will depend on the general level of deficiency in the basal diets of the groups studied. On the other hand, when diets are grossly and generally inadequate, almost any supplement will usually show some results.

Of the many studies of this sort, applied principally to school children, the classic experiment of Mann⁴⁶ in England is still outstanding. Two hundred boys six to ten years of age were studied over a four-year period. The children given a pint of milk daily in addition to the basic diet, which was taken by them and by the control group and which contained some milk, gained in weight and height considerably more than the children not given the milk supplement. They were also considered to be markedly improved in general fitness and in health. Subsequently, a number of well controlled studies led to substantially the same results.

The characteristic changes in the diets of large populations of children in Europe due to famine conditions associated with the recent war have been a general lowering of food intake, without characteristic or special lack of any one specific essential. This is in sharp contrast to the changes during World War I, because of increased knowledge of nutrition and better planning and rationing. A sharp increase in the incidence and severity of rickets in childhood was a principal effect of World War I in Europe, but this was not a prominent result of the later war. The major inadequacies in the diets of children have been in total calories and total protein and in the percentage of protein from animal sources. This combination of deficiencies is well suited to bring out the effects of protein inadequacy on growth, but it does not lead to many cases of specific deficiency diseases. The effects on growth have been said to be hard to recognize because they are insidious and cannot be measured without careful observations before and following the periods of food shortages. The customary brief sampling survey usually fails to detect them or at least to measure them.

DR. SCHATZKI This is not an artefact. It may be the edge of the left lung, but it seems to be far over.

DR. ADAMS The edge seems to be clearly outlined.

DR. SCHATZKI Anteriorly, and I suppose that this is the posterior edge of the lung.

DR. ADAMS A final question. Is the apparent defect in the ribs overlying air in the lung rather than disease in the bone?

DR. SCHATZKI I would say that it is not a defect in the rib.

DR. ADAMS The history for six and a half years with a proved mediastinal shift indicates a chronic intrathoracic disease. As stated in the record symptoms typical of bronchial irritation were present at the onset. Six weeks before the final admission the patient developed signs of bronchial invasion or ulceration as reflected by the increase in the cough and the appearance of rust-colored sputum. These symptoms were not obstructive in character since there was absence of pain or fever, and the process was not causing inflammation or irritation of the pleural surface or interfering with respiratory function. Pain in lung disease practically always comes from irritation at some point of either the visceral or the parietal pleura. The gain of 30 pounds in weight in two years is almost exclusive of carcinoma, in spite of the classic symptoms of initial slight cough with mucoid sputum, later increasing and accompanied by blood. The recurrent bouts of "tonsillitis" seem to be irrelevant to this problem unless one of those episodes had caused a lung abscess. The subsequent course after the last episode is inconsistent with the supposition of lung abscess. He did not have symptoms for the ensuing year, and when the symptoms appeared, he was afebrile and the sputum was neither foul nor purulent.

The initial physical examination is not helpful except that it excludes the presence of marked bronchial obstruction at that time. The description of the x-ray findings at the first admission mentions an area of consolidation. Whether this abnormality was a mass or an area of pneumonitis, it is impossible to say without seeing the films, which are not available. Also, the consolidated area is described as adjacent to the septum. It might be of importance to know which septum, the major or the minor, but again the information is not at hand. It is impossible to account for collapse of the right middle lobe by a lesion in the posterior part of the right upper lobe except by extrinsic pressure from a mass that would have to arise in the region of the lateral segmental bronchus of the right upper lobe. Presumably, as shown by the slightly elevated temperature and slight leukocytosis, there was some associated pneumonitis with mild obstruction at that time. It was the posterior wall of the right main bronchus that was displaced forward by extrinsic pressure. The posterior wall is the membranous or yielding portion of the bronchus. The upper-lobe orifice is described as being in the center of the area of ex-

trinsic pressure. There was a pathologic process in or invading the upper lobe as proved by blood oozing from the upper-lobe bronchus, and this is the first proof that the hemoptysis was coming from the same region as that in which the mass seemed to be localized. The statement that no tubercle bacilli were found in the sputum is assumed to mean that adequate bacteriologic examination of the sputum was done really to exclude that diagnosis, and we will henceforth leave tuberculosis out of consideration. The passage of a bougie into the middle-lobe bronchus without difficulty demonstrates that the right middle lobe was collapsed by extrinsic pressure rather than by an intrinsic mass.

The patient was discharged without a histologic diagnosis but with the following evidence as a matter of record: he harbored a mass originating in, invading or ulcerating into the lateral bronchus of the right upper lobe, pressing on the posterior wall of the right primary bronchus and causing collapse by extrinsic pressure of the lower lobe. The surgical service did not know the man's trouble, did not think he needed surgical treatment, or were afraid to offer it, or the patient refused to accept it. That there was no lack of confidence is attested by the patient's continued visits to the Out Patient Department. That he was unimpressed by the potentialities in his case is suggested by the failure to keep appointments after four months and his claim of freedom from symptoms for the next six years—he was free of symptoms, that is, except for two episodes of coughing blood-streaked sputum, which were widely separated by intervals of four years and one year previous to the second admission. On readmission, he had symptoms and signs denoting enlargement of the mass to sufficient size to cause obstruction of the bronchi and pulmonary suppuration in the right lung, yet bleeding was minimal, sporadic and not daily as in carcinomatous ulceration.

The physical findings are not helpful. One word is puzzling in the sentence in which it is stated that the breath sounds and tactile fremitus were "negative." Tactile fremitus is present or absent, increased or decreased, but how it is "negative," I do not know. Dr. Mallory kindly showed me a diagram found in the record of the physical findings, which were, in brief, those of an obstructed lung. The other hospital's interpretation of fluid extending to the fifth posterior rib is altered by reading of the heavy-exposure film taken at the Massachusetts General Hospital to an interpretation of obstructive atelectasis of the right lung, and that interpretation seems to be supported by the clinical chart, the high temperature and the signs of infection. There was a secondary anemia consistent with the status of the illness and infection. Penicillin was given with no more effect on the fever than might be anticipated with bronchial obstruction present.

The question, then, is resolved into the nature of this tumor mass in a fifty-one-year-old Lithuanian

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

CASE 33151

PRESENTATION OF CASE

First admission A forty-five-year-old Lithuanian leather tanner entered the hospital complaining of a chronic cough and blood-streaked sputum

For about six months before admission the patient had had a slight, chronic cough productive of a small amount of white sputum, especially in the morning Five weeks before entry the cough began to increase, and streaks of rust-colored blood began to appear in the sputum There was no pain, fever, weakness, sweating or dyspnea In the two years before admission the weight had risen from 170 to 200 pounds

For many years recurrent bouts of "tonsillitis" had caused occasional severe sore throat The last of these had occurred a year and a half before admission, at which time the tonsil "broke," discharging blood and pus

On admission the only abnormal physical findings were generalized rhonchi that decreased after coughing and expectoration An x-ray film demonstrated a round area of consolidation in the posterior aspect of the right upper lobe adjacent to the septum, measuring about 5 cm in the transverse diameter The right middle lobe was collapsed On the second day the temperature was 100°F, but afterwards it remained between 98 and 99°F The white-cell count was 12,000, with 76 per cent neutrophils

At bronchoscopy the posterior wall of the right main bronchus was displaced forward by extrinsic pressure The upper-lobe orifice was in the center of the area of extrinsic pressure Blood oozed from the upper-lobe bronchus, and the middle orifice was reddened No tubercle bacilli were found in the sputum A bougie passed into the middle-lobe bronchus without difficulty The lower bronchi were normal At the end of a week the patient was discharged to be followed in the Out Patient Department

Final admission (six years later) In the four months following discharge the patient was seen several times with no change in his status He failed to keep succeeding appointments and was not seen until six years later, when he was referred from another hospital because of fluid in the right side of the chest He claimed to have been free of symptoms, except for two brief episodes of coughing

blood-streaked sputum These occurred, respectively, four years and one year before readmission, and each lasted about a day Six weeks before admission a mild productive cough had developed in association with intermittent rusty streaking of the sputum Four weeks later the patient became feverish, had a headache and felt chilly, although he experienced no frank chill At the other hospital x-ray studies showed "a right hydrothorax rising to the fifth rib posteriorly" Ten to 15 cc of brownish fluid was removed at each of several thoracenteses Penicillin and sulfadiazine were given with no effect on the temperature, which remained elevated After two weeks, the patient was transferred to the Massachusetts General Hospital

Physical examination disclosed an obese, pale, sweating and feverish patient The right side of the chest up to the apex was completely flat to percussion Bronchial breath sounds were audible over the right upper lobe Breath sounds and tactile fremitus were "negative" over the lower lobe and depressed over the middle The left lung was normal Abdominal, rectal and neurologic examinations revealed no significant abnormalities

The temperature was 103°F, the pulse 90, and the respirations 25 The blood pressure was 114 systolic, 64 diastolic

Examination of the blood showed a red-cell count of 4,400,000, with a hemoglobin of 11 gm per 100 cc, and a white-cell count of 8120, with 67 per cent neutrophils The urine, blood sugar, total protein and nonprotein nitrogen were normal On x-ray examination the right lung appeared dense, with the exception of a small aerated area in the upper right portion of the chest The heart and mediastinum were markedly displaced to the right The left lung was clear

In the hospital the temperature spiked from 103 to 104°F every day Abundant colonies of alpha-hemolytic streptococci grew from the sputum Penicillin was started, with no effect on the fever An operation was performed on the tenth hospital day

DIFFERENTIAL DIAGNOSIS

DR RALPH ADAMS* May we see the x-ray films?

DR RICHARD SCHATZKI All the films that were taken are not here, there are no films from the first admission This film shows the mediastinum displaced to the right and air in the apex of the right lung

DR ADAMS Do you consider this area of density to be bony in character?

DR SCHATZKI It looks like it

DR ADAMS Also, on the film the manubrium is outlined, and the trachea is displaced to the right One can postulate a shadow in this region of the tracheal bifurcation that was not mentioned in the record Is that actually something, or is it again an artefact?

*Surgeon Lahey Clinic

ANATOMICAL DIAGNOSIS

Basal-cell papilloma of bronchus, with cornification

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY The bronchoscopic biopsy from this patient gave the laboratory a difficult problem because it was unlike any bronchiogenic tumor we had ever seen or, so far as I know, any that has heretofore been reported. It was obviously epithelial and contained foci of squamous cells and yet did not look like a squamous-cell carcinoma. After struggling several days with it, we finally returned a diagnosis of basal-cell carcinoma with foci of cornification. Our hesitation was largely based on our belief that so-called "basal-cell carcinomas" are actually tumors of the skin

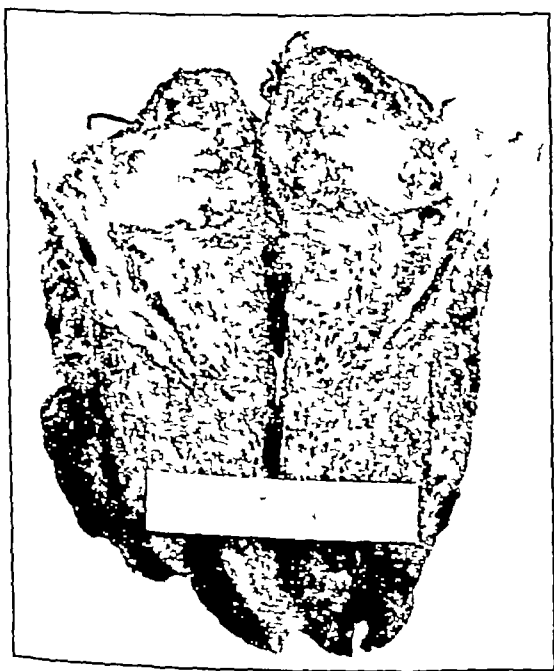


FIGURE 1

appendages and, therefore, should not occur in mucous membranes. In the registry of lung tumors, however, I have seen a case that was indistinguishable from a basal-cell carcinoma of the skin.

When the lung was resected a large endobronchial tumor was found that had spread through the branches of the upper-lobe bronchus (Fig. 1). It was attached to the bronchial wall at one point only and elsewhere could be readily shelled out with the gentlest of blunt dissection. We could make out no invasion of the lung tissue.

In the group of bronchial adenomas reported from the Army Institute of Pathology by Holley* the tumors are classified into two types, the usual form, which strongly resembles a carcinoid of the appendix, and a second glandular or pseudoglandular type, which sometimes resembles closely the tumors

of the salivary glands that have been described as cylindromas. None of Holley's cases, however, resembled the tumor in the case under discussion, in which the majority of the cells were small, basophilic and slightly spindle shaped (Fig. 2).



FIGURE 2

They were oriented at right angles to the stroma. Occasional cells showed various degrees of cornification. The appearances slightly suggested adamantinoma, and one pathologist who saw the sections was willing to make this diagnosis. I finally called the tumor a basal-cell papilloma with cornification. The regional lymph nodes were free from metastasis, and I believe that the prognosis is good.

CASE 33152

PRESENTATION OF CASE

A forty-three-year-old Italian baker entered the hospital because of jaundice.

Eight weeks before entry the patient had begun to have epigastric discomfort after meals, particularly if the food was fatty or fried. He also complained of fatigue, anorexia and "a heavy head" but continued to work at his job. Six weeks before entry he began to have postprandial nausea. On three occasions he vomited about thirty minutes after

*Holley S. W.—Bronchial adenomas. *Mil. Surgeon* 99:528-554, 1946.

leather tanner—a tumor that started like carcinoma, grew like adenoma and looked like a dermoid. The duration of the manifestations of disease, the long periods of freedom from complaint, the gain in weight and the absence of demonstrable metastases lead one to exclude carcinoma from further consideration in the differential diagnosis. If carcinoma was present in this case, it was only as a degenerative end product in a tumor with a different beginning. If the age and sex of the patient are excluded, this case report is a classic description of bronchial adenoma. Patients with such tumors usually have had symptoms of cough and sporadic hemoptysis for many months when first seen by thoracic consultants. They are in general in good health. The x-ray examination shows signs of bronchial obstruction. In a number of years, even if intraluminal tumors are cleared away, bronchoscopically, extraluminal growth may cause extrinsic pressure leading to obstruction and suppuration and, finally, to resection. Most cases occur in women. Seven out of 8 occur in women under forty years of age. This should be compared with carcinoma, in which 3 out of 4 cases occur in men and in which 5 out of 7 are in patients over forty years of age. The incidence of adenoma is 5 to 10 per cent of that of carcinoma, and five-year cures are obtained in 95 to 100 per cent of cases. The five-year curability rate for resectable carcinoma of the lung is around 7 per cent. Other noncarcinomatous tumors of the lung, such as a hamartoma, myxochondroma and sarcoma, have been seen as solitary examples but have shown no similarity helpful to the differential diagnosis in this case. The lateral and posterior displacement of the trachea, the localized calcification of bony density resembling a canine tooth and the area of surrounding rarefaction, instead of solid density that is expected from a solid tumor, cause one to postulate the presence of a dermoid cyst with rupture into the bronchus as the cause of this man's difficulty and the source of the brownish fluid obtained in quantities of 10 to 15 cc at the other hospital on several occasions. The expectoration of hair or the like, debris, fluid or sputum containing cholesterol crystals or fat droplets, however, was not described in the record. Therefore, I shall have to follow the statistical-likelihood precept of the clinician for whom these exercises are named and make a diagnosis of obstructive bronchiectasis of the right lung caused by bronchial adenoma.

DR DONALD S KING Dr Adams, I think that our bad pennies have returned. This is a case that you and I saw in 1940. Dr Schatzki also saw the x-ray films in 1940. I will read the three notes made at that time. Dr Schatzki says, after describing the x-ray films, "I do not believe that this is an abscess. The localized area of collapse in the upper lobe is most probably due to bronchiogenic tumor. This is the likeliest diagnosis."

My note reads, "Diagnosis not yet clear. No definite evidence of tumor. There may have been two pulmonary infarcts, one in July and one in August. Would like to see the patient in the Pulmonary Clinic in four weeks."

You saw him in the Pulmonary Clinic, Dr Adams, and wrote, "Patient continues in good health. Only complaint is blood-streaked, brown sputum about every third morning—small amount, not foul. Believe episodes are decreasing. No pain in chest, no loss of weight or appetite. Patient advised and reassured. To return for a repeat x-ray film."

The patient himself wrote, "I cannot make the appointment to have the x-ray film repeated. Have a bad cold. Will be in when my cold is better." That is the last that was heard from him.

I saw him when he came back last fall, and our diagnosis was the same as yours—an adenoma of the bronchus.

DR CARROLL B MILLER The transcribed history stops at the second bronchoscopy. I am sorry that Dr Benedict is not here to describe the operation. He had a trying time with the patient. He found a spongy, easily bleeding mass, which he biopsied. The patient was difficult to handle at that point. A good deal of blood and tumor was aspirated over into the left bronchus. Dr Benedict had enough of a view of the carina and the two bronchi to tell fairly well that this was a tumor mass that had almost completely obstructed the right main bronchus. The preliminary pathological report of the biopsy was carcinoma. The patient was referred for exploration. We fully expected the tumor to be inoperable because of the diagnosis of carcinoma returned by the Pathology Department and because of the time interval between the first admission and the last, when we opened the chest, however, we found that the upper lobe was completely collapsed, as we expected, and the middle and lower lobes moderately collapsed, but there was no fluid in the chest and, curiously enough, the mass surrounding the upper-lobe bronchus was small. It was decided because of the location that it would be necessary to do a pneumonectomy. I cut across the main bronchus and found in my incision in the bronchus a tongue of tumor extending 3 mm beyond the point of incision. I was able to extend the incision and get completely around the tumor and do a pneumonectomy, with division of the right bronchus. On inspecting the specimen afterward, we found that the attachment of this tumor, so far as the bronchus was concerned, was several millimeters distal to my incision, with a thumblike projection extending up into the bronchus.

CLINICAL DIAGNOSIS

Carcinoma of bronchus?

Adenoma, right-stem bronchus?

DR ADAMS'S DIAGNOSIS

Bronchial adenoma, with obstructive bronchiectasis

more favors an obstructive type of jaundice. I would suppose that by that time the phosphatase would have been elevated if it followed the usual rule in obstructive jaundice. The cholesterol was slightly elevated. The serum amylase was normal, and the bilirubin was elevated, as might have been anticipated with complete jaundice of that duration. Thus far, the onset of jaundice after atypical transient right-upper-quadrant pain, with absence of a palpable gall bladder, and the low alkaline phosphatase favor jaundice of intrahepatic origin. On the other hand, the normal prothrombin time, the negative cephalin-flocculation test and the absence of a palpable spleen may be taken as evidence against the jaundice being due to liver damage.

I am disturbed about the symptoms five or six weeks before the patient became jaundiced. It seems to me — and this is not on the basis of experience really — that five weeks of prodromal symptoms before developing jaundice is rather longer than I should have anticipated with an acute hepatitis. Thus, I am still unable to reach any definite conclusions but am nevertheless forced to try to make a diagnosis that I am perfectly sure is not going to be correct.

I believe that this patient did not have primarily intrahepatic disease, the evidence is more against than in favor of that diagnosis. I do not believe that the symptoms were due to gallstones. It is unusual for a patient of forty-three, with complaints of only eight weeks' duration, to have a history suggestive of gallstones so indefinite as this, beginning with slight epigastric distress and itching and going into a period of fatigue, malaise and "a heavy head" and then nausea and vomiting. That is so unlike uncomplicated gallstones that it would be impossible for me to feel confident about making such a diagnosis in this man.

The patient had a duodenal ulcer. I cannot get away from the fact that this lesion was probably in the duodenum, and again I cannot state definitely why I get that impression. It is probably because I do not believe that he had intrahepatic disease or gallstones. I had hoped that Dr Schatzki would show a large crater or something else and that there had been reaction enough around the ulcer to make it possible for jaundice to have been secondary to that.

Carcinoma of the ampulla of Vater, of course, is perfectly possible, but I cannot make this diagnosis nor can I exclude it.

I must leave this case without a satisfactory diagnosis in my own mind and simply say that the patient had an ulcerating lesion in the duodenum, which in some way was responsible for obstruction to the common duct.

DR TRACY B MALLORY: Are there any suggestions or comments? Dr Giddings, would you give the opinion on the ward?

DR W PHILIP GIDDINGS: We thought definitely that this man had complete obstructive jaundice, as Dr McKittrick has deduced. We also were rather puzzled regarding the pain and the exact nature of the obstruction. The patient had two conditions — complete obstructive jaundice and blood in the stools — that we tried to add up to a carcinoma of the ampulla. He gave a definite history of pain. There was no palpable gall bladder, however, and there was x-ray evidence of an active duodenal ulcer.

DR MALLORY: Will you give the operative findings?

DR GIDDINGS: We operated with a diagnosis of two diseases: common-duct stone and duodenal ulcer. It was quite apparent that the patient did not have gall-bladder disease. The gall bladder was completely normal, but the common duct was greatly dilated — about the size of a man's thumb. At the lower end of it was a readily palpable tumor. The duct was opened and found to contain crystal-clear white bile, and we could visualize within it a tumor mass that had the appearance of carcinoma. This was biopsied, and adenocarcinoma reported. We did a two-stage Whipple procedure, at the first operation transecting the common duct as high as we could beneath the hepatic artery, and performing a routine type of anastomosis. About three weeks later after recovery from the jaundice, we completed the Whipple type of resection, including the head of the pancreas and the duodenum.

CLINICAL DIAGNOSES

Common-duct stone
Duodenal ulcer

DR MCKITTRICK'S DIAGNOSIS

Ulcerating lesion of duodenum, with secondary obstruction of common duct

ANATOMICAL DIAGNOSIS

Carcinoma of common bile duct

PATHOLOGICAL DISCUSSION

DR MALLORY: The specimen that we were finally provided with consisted of the pyloric end of the stomach, a major part of the duodenum, a segment of the common bile duct and a segment of the head of the pancreas. In the common bile duct slightly posterior to the papilla was a primary carcinoma that had extended into the surrounding tissues. We were completely unable to find any trace of duodenal ulcer. I have no explanation for the discrepancy.

DR SCHATZKI: Was anyone from the X-Ray Department present?

DR MALLORY: I cannot answer that.

DR SCHATZKI: The reason I ask is that we have seen cases in which ulcers have entirely disappeared between the time of examination and either operation or autopsy, I think it is inconceivable that there was no ulcer at the time of examination, although it may have healed by the time of resection.

eating Three weeks before entry, while returning from work at 3 00 a m, he was seized with a severe, colicky, right subcostal pain that occurred in spasms lasting five to ten minutes at a time For the next five hours he had many such spasms associated with restlessness, sweating, chills, weakness and nausea He also had occasional stabs of knifelike pain beneath the left scapula That evening his wife noticed that the eyes were yellow During the next few days he rapidly developed generalized jaundice and itching severe enough to keep him awake at times The urine became dark colored and the stools clay colored Passage of the dark urine was associated with burning The patient also became constipated, moving the bowels only every two to four days Two weeks before entry these symptoms had progressed to the point where the patient had to stop working He saw a physician, who prescribed "pills," bed rest and a fat-free diet Five days before entry he began to have chilly sensations, alternating with sensations of warmth He had had no more attacks of colic, but there was some residual soreness in the right upper quadrant He had lost 15 pounds during the two weeks before entry

The patient's health had previously been excellent except for mild exertional dyspnea and some ankle swelling after long hours on his feet

Physical examination revealed an intensely jaundiced, moderately obese man showing multiple scratch marks of the skin The heart and lungs were normal The liver was firm, smooth and moderately tender Its margin was palpated 7 cm below the costal margin in the midclavicular line The spleen was not palpable

The temperature was 98°F, the pulse 60, and the respirations 20 The blood pressure was 140 systolic, 100 diastolic

Examination of the blood disclosed a red-cell count of 5,280,000, with 12 0 gm of hemoglobin, and a white-cell count of 13,000, with 78 per cent neutrophils The serum phosphorus was 4 4 mg, the nonprotein nitrogen 31 mg, the total protein 7 7 gm, the cholesterol 312 mg, and the cholesterol esters 158 mg per 100 cc, and the alkaline phosphatase 3 8 units and the amylase 12 units per 100 cc The van den Bergh reaction was 14 4 mg per 100 cc direct, and 19 0 mg total, and a cephalin-flocculation test was negative after twenty-four hours and + after forty-eight hours The prothrombin time was normal

The urine gave a + test for albumin and a ++++ test for bile Urobilinogen was present in a dilution of 1 8 The stools were slightly yellow and gave a positive guaiac test Examination of the sediment from duodenal drainage showed absence of bile, the sediment contained numerous red cells and white cells A gastrointestinal series showed a constant deformity of the duodenal cap, in the center of which was an ulcer crater The esophagus,

stomach and lower portions of the duodenum were normal Sigmoidoscopy was negative

The patient was placed on hykinone, atropine and a high-protein, high-carbohydrate, high-vitamin diet

On the eleventh hospital day an operation was performed

DIFFERENTIAL DIAGNOSIS

DR LELAND S MCKITTRICK Before seeing the x-ray films, let us summarize the story The patient stated that eight weeks before admission he had had epigastric discomfort, with some malaise and nausea, and that five weeks later he had had attacks of colicky right-upper-quadrant pain — the pains were apparently colicky because they came in spasms, lasting from five to ten minutes He then began to be restless, had chills and some nausea, and developed jaundice Physical examination on entry did not reveal much, except a liver that was slightly low and moderately tender, and x-ray films showed a presumable duodenal ulcer

DR RICHARD SCHATZKI The films show a definite clover-like deformity of the duodenal cap There is evidence of long-standing duodenal ulcer and probably a crater in the area of maximal constriction I cannot see any abnormality in the second portion of the duodenum

DR ARTHUR W ALLEN How large a crater is that?

DR SCHATZKI I am not sure, as a matter of fact, but I should say about 4 mm

DR MCKITTRICK I cannot put this history together and make it add up to any clear-cut diagnosis Perhaps the thing to do is to take an outstanding symptom, which is jaundice, and see if we can reason from that and get somewhere Was this jaundice, which was obviously not the hemolytic type, due to intrahepatic disease or to obstruction of the external biliary tract?

The patient had pain, but the pain was not sufficiently distinctive to mean much to me The jaundice is somewhat confusing — it was apparently complete At least, the patient had clay-colored stools on admission, and there was no bile in the duodenal contents, I take that statement as being evidence of complete jaundice The liver was slightly enlarged and moderately tender, but that again does not give us too much help The spleen could not be palpated If it had been palpable, I think that we could take that as evidence of a process within the liver, but it could not be felt so that we get no help from that No mention is made of a palpable gall bladder — evidence that would permit the assumption that the process was in the extra-biliary tree

The laboratory evidence is slightly confusing I do not know just how frequently a normal alkaline phosphatase is found with obstructive jaundice Certainly an alkaline phosphatase of 15 units or

by some to result in unconsciousness. This drug produces in conscious patients progressive weakness of the eyelids and strabismus with diplopia, followed by weakness of the throat and jaw muscles and the muscles of the extremities and trunk. Overdosage causes complete respiratory paralysis. The last may be a terrifying experience, and the drug should therefore not be used except in combination with a general anesthetic.

In anesthetic practice, curare may be combined with any of the general anesthetic agents, such as nitrous oxide, ethylene and cyclopropane. If it is used with ether or Pentothal, both of which have a curariform action, the dose should be much smaller than when it is combined with the other agents.

If adequate respiratory exchange is maintained, this drug is apparently quite safe. The greatest danger lies in respiratory depression or even respiratory paralysis from overdosage. Curare should never be administered without adequate facilities for maintaining a patent airway and administering artificial respiration. It has been shown that it takes twenty times as much of this drug to kill dogs when artificial respiration is employed as when it is not. Curare is eliminated quite rapidly from the body. Most of it is broken down in the liver, and the remainder is excreted unchanged by the kidneys.

The pharmacologic antidote for curare is prostigmine. It must be remembered, however, that prostigmine must never be given in lieu of the establishment of a patent airway and the administration of artificial respiration, preferably with oxygen. If adequate respiratory exchange and a sufficient supply of oxygen are maintained, the use of prostigmine should never be necessary. Sufficient recovery of the muscles of respiration to carry on adequate respiratory exchange usually takes place within ten to fifteen minutes.

Abdominal relaxation under curare combined with a general anesthetic approaches that obtained with spinal anesthesia, most surgeons, however, believe that actual operating conditions in the abdomen may not be quite so satisfactory as those under spinal anesthesia. Contraction of the bowel, which is evident under spinal anesthesia, is not usually present when a combination of curare and a general anesthetic is employed.

This drug is unquestionably firmly established as an important addition to the already formidable group of anesthetic agents, and when used by anesthesiologists familiar with its advantages and yet acutely aware of its limitations, it can be a valuable aid to modern surgery. Observations regarding its use in two series of patients appear elsewhere in this issue of the *Journal*.

REFERENCES

1. Gill, R. C. Curare misconceptions regarding discovery and development of present form of drug. *Anesthesiology* 7:14-23, 1946.
2. McIntyre, A. R., and King, R. E. d-Tubocurarine chloride and choline esterates. *Science* 97:69, 1943.
3. Bennett, A. E. Preventing traumatic complications in convulsive shock therapy by curare. *J. A. M. A.* 114:322-324, 1940.
4. Griffith, H. R., and Johnson, G. E. Use of curare in general anesthesia. *Anesthesiology* 3:418-420, 1942.

THE INSTITUTE OF SOCIAL MEDICINE AT OXFORD

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Formerly

The Boston Medical and Surgical Journal

Established 1828

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MATERIAL should be received not later than noon on Thursday, two weeks before date of publication

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CURARE

THERE is something spectacular about the introduction of a new drug that immediately achieves for itself a wide field of usefulness. Only slightly less spectacular is the discovery of a new and widespread use for an old drug, to this category belongs curare.

Curare, the ancient arrow poison of certain South American Indians, has been known for over three hundred years. Sir Walter Raleigh is credited with being the first White man to observe its effects. He apparently became acquainted with it during his famous voyage up the Orinoco in 1595. The ability of curare to effect muscular relaxation and loss of tone by paralysis of the myoneural junction has been known for many years. In fact, no less a person than Claude Bernard established this fact experimentally and suggested the therapeutic use of curare in hydro-

phobia, chorea, tetanus and epilepsy. For many years after his investigations, curare remained essentially a pharmacologic curiosity and a physiologist's tool for the demonstration of the existence of the myoneural junction as a physiologic entity.

To Mr. Richard C. Gill must go the credit for many modern conceptions concerning this drug. Mr. Gill spent a great deal of time in the Amazonian jungles, and it was he who first brought to this country, in 1938, adequate supplies of the drug for accurate assays and standardization. He¹ has recently pointed out that curare is not derived from a single species of plant but is a mixture of botanical components widely distributed throughout both North and South America, more particularly in the region around the Amazon River. McIntyre² and Bennett,³ of the University of Nebraska, were the first to investigate modern curare pharmacologically and to submit it to clinical trial.

Following the investigations of McIntyre and Bennett, curare was first used in the field of psychiatry in an attempt to overcome some of the less desirable side effects of convulsive shock therapy in the treatment of various psychoses. Since the forceful muscle contractions associated with this type of therapy not infrequently resulted in fractures and muscle rupture, it was desirable to have some method of lessening their severity.

Griffith and Johnson,⁴ of Montreal, introduced this drug into the field of anesthesiology in 1942. Their initial report of its use in twenty-five surgical operations was extremely promising. Since that time, many workers in laboratories and clinics have reported favorably on the benefits to be derived by a combination of a general anesthetic, to render the patient insensible to pain, and the intravenous injection of curare, to provide muscular relaxation.

Recent work in the laboratory with this drug has confirmed the statement of Claude Bernard that the primary action was at the myoneural junction. With adequate doses, curare so completely blocks the myoneural junction that the muscles no longer respond either to mechanical stimulation or to the injection of acetylcholine. Curare does not affect nerve conduction.

Curare is not an anesthetic agent or a hypnotic, although the administration of large doses is said

by some to result in unconsciousness. This drug produces in conscious patients progressive weakness of the eyelids and strabismus with diplopia, followed by weakness of the throat and jaw muscles and the muscles of the extremities and trunk. Overdosage causes complete respiratory paralysis. The last may be a terrifying experience, and the drug should therefore not be used except in combination with a general anesthetic.

In anesthetic practice, curare may be combined with any of the general anesthetic agents, such as nitrous oxide, ethylene and cyclopropane. If it is used with ether or Pentothal, both of which have a curariform action, the dose should be much smaller than when it is combined with the other agents.

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- 3 Bennett, A. E. Preventing traumatic complications in convulsive shock therapy by curare. *J. A. M. A.* 114:322-324, 1940.
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The early years of the Institute have had to do with the organization of a number of worthwhile projects. An investigation has been undertaken to study the development, health and sickness ex-

perience of a relatively large group of children up to the age of five. In collaboration with local factories, the Institute is investigating occupational morbidity to sickness and industrial hazards. A survey of how thyroid enlargement in school children is related to the iodine content of drinking water is being carried out extensively in several districts of England and Scotland. X-ray studies of growth and development of bone are being made. In connection with human genetic studies, a pilot survey of forty-two sets of twins of school age has been completed. Statistical analyses of stillbirth rates and neonatal death rates in certain counties and county boroughs are being made. Other activities have included problems in connection with confinement among women of the working class, health examinations, consultative work and the teaching of students in their clinical years at Radcliffe Infirmary. Perusal of the *First Annual Report*¹ suggests that the Institute is attempting to fill in the gaps left by governmental public-health methods of collecting and recording health statistics. Surely, if adequate methods of recording illnesses were put into practice, the work of statistical epidemiology would be much simpler than it is at present.

In his report, Professor Ryle speaks of "social pathology" in contrast to "human pathology," defining the former as follows: "The advancement of our knowledge of man in health and disease and the investigation of the social causes of disease." Incorporated in the concept is the study of the healthy state and of the borderland involving disease. It is not difficult to realize that equal knowledge for human welfare will accrue from directing attention to factors having to do with healthy groups, as with those concerned with diseased groups, and that these are appropriately co-operative fields of investigation.

Elsewhere, Professor Ryle² has stated a point of view that deserves repeating again and again:

We are most of us conscious of the fact that medicine during the past quarter of a century has become (inevitably, be it allowed) not merely more specialized but also more technical, and that in the process—for the technicalities are often precise, intricate and time-consuming—the old aetiological interest and humanism of our fathers have tended to take the second place. In the teaching hospitals this can scarcely be disputed. Investigation to the limit, mainly by objective methods and often with

too little said to or done for the patient during or after the tedious process, has been the prevailing trend, especially in the case of the more chronic or seemingly more obscure varieties of disorder and disease. More and more accurate assessments of local pathology, with the help of more and more colleagues and instruments, and less and less intimate understanding of the patient as a whole man or woman with a home and anxieties and economic problems and a past and a future and a job to be held or lost, have become the order of the day. As we direct our students, so in large measure must the outlook and method of each new generation of doctors be determined.

Professor Ryle, who was formerly Regius Professor of Physic at Cambridge University, recently visited Boston, having given an address at the Harvard Medical School on February 24. His remarks centered about the need for a better understanding of normal variations. He sketched some of the methods that the Institute of Social Medicine is employing to attain this result. Those who met and heard Professor Ryle were deeply impressed. His undertaking deserves success, and it is suggested that his institution serve as a model for needed research activities in this country.

REFERENCES

1. *First Annual Report 1945*. 20 pp. Oxford, England: University Press, 1945.
2. Ryle, J. A. Social medicine: its meaning and its scope. *Brit M J* 2: 633-636, 1943.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BIGELOW—Enos H. Bigelow, M.D., of Framingham died March 13. He was in his ninety-second year.

Dr. Bigelow received his degree from Harvard Medical School in 1882. He was a former president of the Massachusetts Medical Society and a former chairman of the Framingham Board of Health.

EMERY—Edward S. Emery, Jr., M.D., of Brookline died March 16. He was in his fifty-fourth year.

Dr. Emery received his degree from Harvard Medical School in 1920. He was an instructor at Harvard Medical School, as well as senior associate in medicine, Peter Ben Brigham Hospital, and medical consultant, Bedford Veterans Hospital. He was a member of the American Society for Clinical Investigation, American Gastro-Enterological Association and International Society for Gastro-Enterology and a fellow of the American Medical Association.

His father, his widow, two sons and a daughter survive.

EWING—Edward H. Ewing, M.D., of Stoughton, died March 8. He was in his seventy-fifth year.

Dr. Ewing received his degree from the College of Physicians and Surgeons, Baltimore, in 1897.

His widow survives.

HAYES—Arthur Warren Hayes, M.D., of Greenfield died March 11. He was in his fifty-sixth year.

Dr. Hayes received his degree from Middlesex University School of Medicine in 1920. He was a member of the New England Roentgen Ray Society, the Radiological Society of North America and the American College of Radiology, and was a fellow of the American Medical Association.

A sister and six brothers survive.

HILLS—Charles E. Hills, M.D., of Natick, died February 23. He was in his seventy-eighth year.
Dr. Hills received his degree from Dartmouth Medical School in 1901. He was a fellow of the American Medical Association.
His widow, a son and three daughters survive.

RYDER—George H. Ryder, M.D., of Quiney, died March 12. He was in his seventy-third year.
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CORRESPONDENCE

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There is an unfortunate tendency to accept thyroidectomy as an entirely satisfactory method of treatment, and it is true that in the best surgical clinics the operative mortality is extremely low. But the hoarseness of recurrent laryngeal nerve paralysis, the twitch and spasm of tetany and the apathy and lethargy of myxedema are seen with sufficient frequency in patients bearing the mark of the thyroid surgeon to emphasize the fact that the surgical treatment of hyperthyroidism is something less than ideal. Moreover there are patients who continue to exhibit the symptoms and signs of thyrotoxicosis despite one or two operations. Finally, any operation implies a certain amount of danger, discomfort, disability and financial loss. In brief, it is self-evident that any nonsurgical procedure is superior to a surgical one, provided the benefits and the risks are at least equal.

The crucial question, then, is, Have we a safe and effective nonsurgical method for treatment of hyperthyroidism? The answer, I believe, is a vigorous affirmative! In Dr. Frank H. Lahey's paper, "Surgery of the Thyroid Gland," which appeared in the January 9 issue of the *Journal*, he groups propylthiouracil with thiouracil and thioabarbital and repeatedly refers to them collectively as "dangerous drugs." This is an unfortunate and entirely misleading method of discussion. One would not consider gramicidin and penicillin together and refer to them as "dangerous." Each drug requires analysis and classification according to its own merit and its own individual toxicity and propylthiouracil deserves critical evaluation alone, not in the company of its "dangerous" brothers. Propylthiouracil has now been used for nearly two years in several thousand patients. The mortality in the patients receiving the drug is zero. A few minor reactions have been reported, none of which required that the drug be discontinued. No clear case of agranulocytosis has yet been encountered. Undoubtedly more toxic effects will be observed in the future as the use of this chemical increases, but the rate will surely be very small. Except for penicillin it is difficult to name an agent at once so potent and innocuous in the whole field of therapeutics!

Is the drug entirely effective? One must be more cautious in answering this question because the time elapsed since its introduction does not permit a categorical answer. But it appears quite certain that propylthiouracil is effective in reducing the metabolic rate—a controllable "medical thyroidectomy"—within a fairly short period in virtually every patient.

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We are most of us conscious of the fact that medicine during the past quarter of a century has become (inevitably, be it allowed) not merely more specialized but also more technical, and that in the process—for the technicalities are often precise, intricate and time-consuming—the old aetiological interest and humanism of our fathers have tended to take the second place. In the teaching hospitals this can scarcely be disputed. Investigation to the limit, mainly by objective methods and often with

too little said to or done for the patient during or after the tedious process, has been the prevailing trend, especially in the case of the more chronic or seemingly more obscure varieties of disorder and disease. More and more accurate assessments of local pathology, with the help of more and more colleagues and instruments, and less and less intimate understanding of the patient as a whole man or woman with a home and anxieties and economic problems and a past and a future and a job to be held or lost, have become the order of the day. As we direct our students, so in large measure must the outlook and method of each new generation of doctors be determined.

Professor Ryle, who was formerly Regius Professor of Physic at Cambridge University, recently visited Boston, having given an address at the Harvard Medical School on February 24. His remarks centered about the need for a better understanding of normal variations. He sketched some of the methods that the Institute of Social Medicine is employing to attain this result. Those who met and heard Professor Ryle were deeply impressed. His undertaking deserves success, and it is suggested that his institution serve as a model for needed research activities in this country.

REFERENCES

- 1 *First Annual Report 1945*. 20 pp. Oxford: England University Press, 1945.
- 2 Ryle, J. A. Social medicine: its meaning and its scope. *Brit M J* 2: 633-636, 1943.

MASSACHUSETTS MEDICAL SOCIETY

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A sister and six brothers survive.

HILLS—Charles E. Hills, M.D., of Natick, died February 23. He was in his seventy-eighth year.
Dr. Hills received his degree from Dartmouth Medical School in 1901. He was a fellow of the American Medical Association.
His widow, a son and three daughters survive.

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scrub typhus and psittacosis" is incorrect with reference to Rocky Mountain spotted fever. About 80 per cent of the convalescent sera taken fourteen days or more after the onset of rickettsialpox were positive for Rocky Mountain spotted fever in significant dilutions. In nearly all cases, however, the titer was lower when tested with the heterologous antigen than with the homologous antigen.

Possibly also worth mentioning is the misspelling of my name, both in the text and in the references. The consistent manner in which it is misspelled suggests that it is a matter of firm conviction.

ROBERT J HUEBNER,
S A SURGEON

National Institute of Health
United States Public Health Service
Bethesda 14, Maryland

The information regarding the spleen and complement-fixation tests was obtained from the October, 1946, issue of the *Quarterly Bulletin* of the New York City Department of Health, but the facts as they are given in Dr Huebner's letter are clearly stated in his papers that appeared in November, 1946, issues of *Public Health Reports*. The misspelling of Dr Huebner's name was inexcusable, and for this, due apology is offered. — Ed

BOOK REVIEWS

Six Problems of the Returned Veteran. By Howard Kitching, MD. With a foreword by Ernest R Groves. 12°, cloth, 124 pp. New York: Emerson Books, Incorporated, 1946. \$1.50.

This is another book that deals with the returning veteran. It is short and is essentially a practical book. It restates much that has been said in the press and on the stage about the return of Ulysses after his Odyssey, but it presents the material compactly and in a readable manner. This book is not profound, but it abounds in common sense and emphasizes the obvious and the logical.

A reading of this volume may help to reassure persons with mild anxiety by helping them to realize that the difficulties encountered in sexual adjustments after prolonged absence from home are frequent problems with certain stock angles and well known solutions. If it serves to do even that much, its publication is well worth while. In the hands of an intelligent person, this book may do even more because of its simplicity and inclusiveness. The material is well organized.

Diseases of the Retina. By Herman Elvyn, MD. 8°, cloth, 57 pp., with 170 illustrations. Philadelphia: Blakiston Company, 1946. \$10.00.

All ophthalmologists and internists who have mastered ophthalmoscopic technic will derive much aid and considerable satisfaction from this work, which lists forty-two retinal entities catalogued in the eight sections of the book. The clinical course, complications, hereditary characteristics, pathogenesis and treatment of each entity are discussed. Of the one hundred and seventy illustrations, nineteen are in color. Each section carries its own bibliography, which facilitates reference to the authorities.

The main strength of this work, in the opinion of the reviewer, consists in the careful correlation between the clinical and the pathological aspects of each entity, and in the general clarity of the text.

The book would probably lose little and gain much if the last two sections were omitted, and the thirty-two pages thus released were devoted to the following items: an acceptable discussion of the metabolism of the retina, its dependence on the chorocapillaries, its anatomy, its physical and colloidal chemistry, as well as its photochemistry, its oxidation mechanism, the functioning of its capillaries under the pressure levels prevailing in the eye and the fragility and permeability of its capillaries—the references on Page 6 to the work of Hueck do not tell the whole story, and an attempt to interest and to inform the neurologist and the ophthalmologist who are given one brief paragraph on papilledema on Page 54, no charts of scotomas resulting from the retinal entities and no discussion of toxins or processes that affect the retinal ganglion cells or the papillomacular

Diagnostic Examination of the Eye Step-by-step procedure. By Conrad Berens, MD, and Joshua Zuckerman, MD, C M. 8°, cloth, 711 pp., with 410 illustrations. Philadelphia: J B Lippincott Company, 1946. \$15.00.

This clinical vade mecum, analyzing step by step the proper procedure in handling the eye patient, from the history taking down through the entire examination according to approved modern methods, should be in the hands of every young ophthalmologist when he starts the practice of the specialty. As he acquires experience and judgment, the ophthalmologist will find the short cuts to information essential to proper diagnosis and treatment. The established ophthalmologist will gain a wealth of useful, detailed information from the pages of this systematic and encyclopedic volume. The illustrations are well reproduced, and many are in color.

Music in Medicine. By Sidney Licht, MD. 8°, cloth, 132 pp. Boston: New England Conservatory of Music, 1946. \$3.00.

Physicians are cast in a unique role in modern society. They see many persons who are in need of emotional outlets in addition to treatment of whatever physical disorders they may have. The words of doctors of medicine carry so much suggestive power that it is regrettable that some fail to use this power constructively. Many facilities available for psychologic healing are neglected. Dr Licht believes that music is particularly curative and has a unique and important place in medicine. In support of this opinion, he has gone through the existing literature on this subject and has made in addition many fresh observations of his own. He has organized the material systematically into an interesting volume that emphasizes the deeper psychologic uses as well as the more conventional, superficial advantages that music offers the receptive person. This practical and pleasant book will appeal particularly to physicians and patients who are inclined to make the most of social resources that are close at hand.

Dr Licht writes in an informal and graceful manner. His style is provocative and spontaneous. In this book he shows appreciation of psychologic medicine as well as of music. Many people have used symphony concerts for years as a form of self-administered psychotherapy. With the radio and with music better recorded and more cheaply available than ever before, this book is especially timely.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Surgical Treatment of the Nervous System. Supervising editor: Frederic W. Bancroft, MD, associate clinical professor of surgery, Columbia University College of Physicians and Surgeons, attending surgeon, New York City and Beth David hospitals, consulting surgeon, Veterans Administration, Lincoln and Harlem hospitals, New York City, and Kings Park State Hospital, Kings Park, New York; associate editor: Cobb Pilcher, MD, associate professor of surgery, Vanderbilt University School of Medicine, and visiting surgeon, Vanderbilt University Hospital, Nashville, Tennessee. 4°, cloth, 534 pp., with 293 illustrations and 5 color plates. Philadelphia: J B Lippincott Company, 1946. \$18.00.

Pneumoperitoneum Treatment. By Andrew L. Banyai, MD, associate clinical professor of medicine, Marquette University Medical School. 8°, cloth, 376 pp., with 74 illustrations and 16 tables. St. Louis: C V Mosby Company, 1946. \$6.50.

Neurosis and the Mental Health Services. By C P Blacker, MD, FRCP. With a foreword by Sir Wilson Jameson, KCB, MA, MD, LL D, FRCP, chief medical officer of the Ministry of Health and the Ministry of Education. 8°, cloth, 218 pp., with 56 tables. New York: Oxford University Press, 1946. \$5.00.

thiouracil alone is the method of choice in the treatment of hyperthyroidism

RALEIGH W BAIRD, JR., M.D.

53 Greenough Street
Brookline, Massachusetts

* * *

The above letter in its original form concluded with the sentence, "It seems logical to conclude that thyroidectomy for hyperthyroidism deserves a place in the surgical graveyard, when other outmoded procedures rest in uneasy peace." This was forwarded to Dr Frank H Lahey, who was later informed that Dr Baird had requested that the last sentence be changed to read as printed. Dr Lahey's reply is as follows:

To the Editor Dr Baird's conclusion that subtotal thyroidectomy is outmoded in the treatment of hyperthyroidism since the advent of newer antithyroid drugs seems premature. He admits that the evidence at hand does not allow a definite statement concerning the problem of remission or recurrence on withdrawal of the drug, be it either thiouracil or propylthiouracil. The incidence of prolonged remission after the withdrawal of treatment with these drugs in patients with severe or moderately severe hyperthyroidism has, in our experience, been extremely discouraging. We agree, and have so reported, that these drugs produce remissions in patients with mild hyperthyroidism who have small goiters.

His statement that propylthiouracil can be given without danger is not substantiated by facts. There is even danger in its short-term use, as we have used it. We have observed significant blood changes in 5 of 370 patients treated with propylthiouracil. One was a typical severe case of agranulocytosis, and a fatality was prevented by energetic treatment with penicillin. The danger of development of sensitivity from repeated courses of treatment, should a relapse develop, needs further evaluation, as does the possible danger of grave histopathologic changes following prolonged maintenance treatment.

Since no hope for restoration of the thyroid gland to normal size and structure can be held by virtue of the use of these drugs, it is evident that their action cannot be curative. On the other hand, it has been our experience in a series of 750 cases that either thiouracil or propylthiouracil is entirely effective in returning the basal rate to normal in every case if given in a large enough dose over a sufficient length of time.

The possible dangers of unskillful thyroid surgery have been the basis of numerous papers from this clinic, and we are well aware of such dangers. A blanket condemnation of thyroidectomy as a useful procedure on the basis of these dangers, which can be circumvented, seems to lack logic. Similar condemnation of gall-bladder surgery because of possible injury to bile ducts may be made with this type of reasoning. There are a great many places all over the country where safe thyroid surgery is being done.

We are given the responsibility of restoring to health, in the shortest possible time, approximately 560 hyperthyroid patients each year. As our experience has shown that proper preparation of the patient with antithyroid drugs followed by thyroidectomy offers the best chance of restoration to health with minimal operative risk and morbidity and low recurrence rate, we expect on the basis of present knowledge to continue this type of treatment. This plan of treatment eliminates the uncertainty of cure that is inherent in treatment with antithyroid drugs. We shall continue to give patients with mild hyperthyroidism with small goiters or with recurrences the benefit of a trial with iodine or antithyroid drugs in the hope of inciting a remission.

FRANK H LAHEY

605 Commonwealth Avenue
Boston 15

store, in the garage, post office and hospital and on the street the arm describes the same arc. These people say, "Doctor, right here is the trouble." They get me out of bed in the early morning to tell me about it. When I go to bed at night if I go to bed, they are still telling me about it. They tell me not only about themselves, with the minutest detail, but also about all the other members of their families who have the bug and about all their relatives in Boston or New York or some other place who have been sick. They don't stop there; they go back a generation and tell me how they and their families suffered in 1918.

Three weeks ago a miracle occurred. The telephone hardly rang for two days. Only one or two came to the office. I said to myself, "The epidemic is over. It has been pretty tough, but a doctor has got to go through those things once in a while. Life isn't so bad after all." The sun shone brightly on those two days, the sky was a brilliant blue, and the air was like wine. "I shall relax," I said, "and work on the farm, I shall go to see my friends and gaze at the mountains beyond our valley."

I was never more deluded in my life. On the third day the telephone began to ring again, the office filled up, and the daily grind of getting in and out of a car and reaching for the little black bag was just as it had been. The arm began to describe the same quarter circle. Nothing was different except that the complaints became louder and the response to treatment wasn't so good. They told me about this in no uncertain terms and wanted to know whether I had made a mistake in the medicine and what I was going to do about it.

Two or three weeks ago I ventured out on the street. I never do that any more. I never get out of my car except when I go to the office or am making a call. It is too risky. I can't walk a quarter of a block without someone stopping me and saying, "Doctor, my husband is sick. Won't you drop around and see him?" I regard her with a dead-pan look and say, "What is the matter with him?" — all the time watching for that right arm to begin to move. "He has the flu, I guess." "What is his temperature?" "One hundred and two." "That is nothing," I say, "I should be alarmed if he didn't have a fever, some of them have a temperature of 104 or 105." (This last statement is a slight exaggeration, but there is method in it.) "But Doctor, he has an awful headache." "That is perfectly normal," I say. "They all have awful headaches. It will let up soon." "But Doctor, his cough. I am afraid it will settle on his lungs. He has weak lungs, you know. The trouble seems to be up here now." Then I see the right arm begin to move. I am licked, and after wasting ten minutes in a vain effort to get out of making a call, I go to see him.

So I have given up walking on the streets. I don't go into stores any more. If I have anything to buy, I go to the neighboring town. Sometimes it is absolutely necessary to go to the local drugstore. I slink in, keeping close to the wall, and taking advantage of any cover that presents itself until I reach the prescription desk, where I am safe. When I go out I make a plunge for the door with my head down, like a halfback going through the line.

If there was any milk of human kindness in me, there isn't any now. I am as about as sympathetic as a fish, and I look on the human race with fear and aversion. I never smile any more. I never say anything unless it is absolutely necessary. When someone asks me how I am, I say, "Fine, thank you." I wouldn't ask them how they are for any amount of money. One can't risk the consequences of a question like that.

I have gone into my symptoms and mental state in some detail, because I thought that you would want to know all the facts pertaining to my case.

NEIL C STEVENS

Walpole, New Hampshire

RICKETTSIALPOX

To the Editor The editorial "A New Rickettsial Infection in New York City," which appeared in the January 9 issue of the *Journal* was excellently written and quite informative.

I was particularly interested in the statement that in rickettsialpox the spleen is "palpable in about half the cases." I was aware that in some cases a palpable spleen had been reported, but I have as yet seen no data that could be made the basis for calculating the percentage of palpable spleens that occur in rickettsialpox.

The statement "Complement-fixation tests were negative for typhus fever, Rocky Mountain spotted fever, O fever,

A COMPLICATION OF THE "FLU" EPIDEMIC

To the Editor I have lately begun to show rather alarming symptoms. If the "flu" epidemic continues much longer, I am sure I shall become deranged. If you hear that I am standing on a street corner somewhere describing a quarter of a circle with my right arm and ending with the tip of the index finger an inch below the larynx, you will know the worst has happened. All day long I see nothing but that right arm happen. It is impossible to escape it. In every house and

The New England Journal of Medicine

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Volume 236

APRIL 17, 1947

Number 16

THE VALUE OF IMPONDERABLES*

REGINALD FITZ, M.D.†

BOSTON

EVERY medical student is familiar with the Ether Dome of the Massachusetts General Hospital and the words beginning, "On October 16, 1846, in this room, then the operating theater of the Hospital, was given the first public demonstration of anesthesia to the extent of producing insensibility to pain during a serious surgical operation." I have often wondered how knowledge of this achievement spread over the world so promptly—largely, it seems to me, through a strange combination of the two imponderables chance and friendship.

Dr William Morton was a dentist, young and ambitious, poor and struggling hard to obtain a foothold in Boston. He was an ingenious person in a region where bad teeth were frequent so that he quickly managed to achieve distinction as a maker of false ones. From his early days he had a flair for publicity, and soon after entering practice he formed the habit of advertising in the newspapers, in this way he grew to be friends with one of the shrewdest reporters—a man named Albert Tenney,‡ of the *Boston Evening Journal*.

The newspapers made interesting reading. In the fall of 1846, besides realizing that Dr Morton could provide a reliable and handsome set of false teeth by a new process, one might have picked up what little needed to be known of the events on the periphery of a universe of which Boston was clearly the hub, in addition to keeping comfortable track of the deaths or other misadventures of one's friends, one might have discovered that early in November the new building of the Harvard Medical School on North Grove Street was to be opened.

The *Boston Evening Journal* came out in the late afternoon and gave the news in a chatty fashion, easy to read while one's head nodded after supper

as one sat by the table in the parlor where the reading lamp was placed. When you got home on Thursday evening, October 1, and glanced through the paper, your fancy, I trust, was caught by the following item:

We would call the attention of our readers to the advertisement of W. T. G. Morton, Dentist, No. 19 Tremont Row. This gentleman has been very successful in his practice in the city. Last evening, as we were informed by a gentleman who witnessed the operation, an ulcerated tooth was extracted from the mouth of an individual, without giving him the slightest pain. He was put into a kind of sleep, by inhaling a preparation, the effect of which lasted for about three-quarters of a minute, just long enough to extract the tooth. The gentleman, who detected the principal ingredient of the preparation by its odor, states that the use of it is entirely free from danger.

You had no way of knowing that here was reported the astonishing adventure that Mr Eben H. Frost had experienced. Nor, unless you had the imagination of Dr Morton, Mr Tenney and young Dr Henry J. Bigelow, did you appreciate, as Dr Waterhouse might have remarked, that here was something curious in the medical line—a painful surgical operation conducted painlessly. Most probably you merely glanced at the paragraph, yawned rather scornfully, and remarked to your wife that Dr Morton was going much too far in his efforts to get patients.

The Saturday, October 17, issue, however, printed something much more startling. Now you read a paragraph that was almost incredible:

Successful Operation. Yesterday morning, Dr Morton, Dentist, No. 19 Tremont Row, at the invitation of Dr Hawwood, visited the McLean Hospital, and administered his preparation to produce sleep, to a person about to undergo the operation of the extraction of a tumor from the neck. We learn from a gentleman who conversed with one of our oldest and most respected physicians who witnessed the operation, that the success of Dr Morton's experiment was complete. The patient sitting in a chair, with every thing made ready by Dr Warren who extracted the tumor, inhaled the preparation for a very brief space of time, when he fell into a quick slumber, and the surgeon proceeded to extract the tumor. The patient did not manifest the slightest symptoms of suffering, and no muscular action whatever. He appeared to be totally insensible to what was going on, till very near the close of the operation, which was quite protracted, when he drew a long sigh. It is quite as much for the in-

*Presented at a symposium "The Hospital in the Community" held during the Ether Day Centenary of the Massachusetts General Hospital, Boston, October 16, 1946.

†Lecturer on the history of medicine, Harvard Medical School consulting physician, Peter Bent Brigham Hospital.

‡Mr. Tenney became one of the leading newspaper men of Maine, always progressive in matters affecting public good and untiring in his efforts to correct public abuse. A good account of his life is found in the literary records of the graduates of Bowdoin College and the Medical School of Maine for the year ending June 1, 1895 (Number 6, second series).

Oral Medicine By Lester W Burket, M D, D D S, professor of oral medicine, Thomas W Evans Museum and Dental Institute School of Dentistry, University of Pennsylvania, and professor of oral medicine, Graduate School of Medicine, University of Pennsylvania With a section, "Oral aspects of aviation medicine," by Major Alvin Goldbush, A U S, D D S, M S, D S 8°, cloth, 674 pp., with 350 illustrations Philadelphia J B Lippincott Company, 1946 \$12 00

The Modern Treatment of Diabetes Mellitus Including practical procedures and precautionary measures By William S Collens, M D, chief, Diabetic Clinic and Clinic for Peripheral Vascular Diseases, and associate visiting physician, Israel Zion Hospital, Brooklyn, associate visiting physician, Greenpoint Hospital, Brooklyn, attending metabolist, Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, and consultant in metabolic diseases, Rockaway Beach Hospital, New York, and Louis C Boas, M D, assistant in Diabetic Clinic and in Clinic for Peripheral Vascular Diseases, Israel Zion Hospital, Brooklyn, chief, Diabetic Clinic, and assistant visiting physician, Greenpoint Hospital, Brooklyn, and associate in Department of Metabolism, Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn 8°, cloth, 514 pp., with 195 illustrations Springfield, Illinois Charles C Thomas, 1946 \$8 50

Report on a Survey of Medical Education in Canada and the United States By C E Colman, M R C S (Eng), L R C P, M B, B S, M R C P, D P H, Ph D (Lond), and F A P H A, professor and head, Department of Bacteriology and Preventive Medicine and Department of Nursing and Health, director, Division of Laboratories, Provincial Board of Health, and research member, Connaught Medical Research Laboratories, University of Toronto 4°, paper, 53 pp., with 2 tables Toronto University of Toronto, 1946

Motor Disorders in Nervous Diseases By Ernst Herz, M D, instructor in neurology, Columbia University College of Physicians and Surgeons, and Tracy J Putnam, M D, professor of neurology and neurologic surgery, Columbia University College of Physicians and Surgeons 8°, cloth, 184 pp., with 250 illustrations New York King's Crown Press, 1946 \$3 00

Diabetes A concise presentation By Henry J John, M D 8°, cloth, 300 pp., with 74 charts and 44 tables St Louis C V Mosby Company, 1946 \$3 25

Narco-Analysis A new technique in short-cut psychotherapy a comparison with other methods and notes on the barbiturates By J Stephen Horsley, deputy medical superintendent, Dorset Mental Hospital 12°, cloth, 134 pp New York and London Oxford University Press, 1943 \$2 50

Group Psychotherapy Theory and practice By J W Klapman, M D, member, faculty of Northwestern University Medical School, member, Board of Psychiatry and Neurology, and staff member, Institute for Juvenile Research, Chicago 8°, cloth, 344 pp., with 14 illustrations New York Grune and Stratton, 1946 \$4 00

Technique of Psychoanalytic Therapy By Sandor Lorand, M D, member, faculty of New York Psychoanalytic Institute 8°, cloth, 251 pp New York International Universities Press, 1946 \$3 50

Nutrition and Chemical Growth in Childhood Volume II Original data By Icie G Macy, Ph D, Sc D, director, Research Laboratory, Children's Fund of Michigan, member, Food and Nutrition Board, National Research Council and consultant for nutrition to the pediatric staff, Children's Hospital of Michigan With a foreword by Lawrence Reynolds, M D, editor, *American Journal of Roentgenology and Radium Therapy*, and a supplement by Julia O Holmes, Ph D, presenting data collected in the Department of Home Economics, Agricultural Experiment Station, College of Agriculture, University of Illinois 8°, cloth, 1027 pp., with 705 illustrations and 474 tables Springfield, Illinois Charles C Thomas, 1946 \$10 00

Human Ear in Anatomical Transparencies Descriptive text by Stephen L Polyak, M D, professor of anatomy, University of Chicago, anatomic transparencies and illustrations by Gladys McHugh, medical illustrator, University of

Chicago Clinics, and anatomic preparations by Delbert E. Judd, M D, assistant professor of otolaryngology, University of Chicago 4°, cloth, 136 pp., with 83 illustrations Elmsford, New York Sonotone Corporation, 1946 \$10 50

Preventive Medicine and Public Health By Wilson G Smilie, M D, D P H, Sc D (hon), professor of public health and preventive medicine, Cornell University Medical College, New York 8°, cloth, 607 pp., with 41 illustrations and frontispiece and 21 tables New York Macmillan Company 1946 \$6 00

NOTICES

CUTTER LECTURE

The Cutter Lecture on Preventive Medicine will be given at 5 p m on Tuesday, April 22, in the Amphitheater of Building D of the Harvard Medical School Dr Thomas M. Rivers, director of the Hospital of the Rockefeller Institute for Medical Research, New York City, will speak on the subject "Certain Public Health Aspects of Infectious Diseases"

The medical profession, medical and public-health students and others interested are cordially invited to attend

BOSTON UNIVERSITY SCHOOL OF MEDICINE ALUMNI ASSOCIATION

The annual alumni meeting and scientific program of Boston University School of Medicine will be held on Friday, May 9

The scientific program will be held in the auditorium of the medical school The lectures will be open to the medical profession

PROGRAM

- 10 00 a m The Treatment of Congestive Heart Failure
Dr Norman H Boyer
- 10 30 a m The Clinical Use of Benadryl and Pyrazinamide Dr Francis C Lowell
- 11 00 a m Newer Concepts in the Management of Asthma Dr John J Curry
- 11 30 a m The Clinical Uses of Folic Acid Dr Joseph F Ross
- 2 00 p m Recent Developments in the Treatment of Peptic Ulcer Dr Franz Ingelfinger
- 2 30 p m The Use of Anesthetic Procedures in Diagnosis and Therapy Dr Julia Arrowood
- 3 00 p m The Management of Acute Renal Insufficiency
Dr Charles Burnett
- 3 30 p m The Problem of the "Sore Throat." Dr Louis Weinstein

The annual meeting and banquet of the Alumni Association will be held at 7 p m in the Georgian Room, Hotel Statler The guest speaker will be Francis W Dahl, well known cartoonist of the *Boston Herald*, whose subject will be "Dahl Looks Things Over" Daniel L Marsh, president of Boston University, will greet the alumni Alex J McFarland, secretary of the Class of 1930 of Dartmouth College, will speak on the subject "Dartmouth Alumni Plan" Dean Donald Anderson, of the medical school, will give a progress report Dr Roger M Burgoyne, president of the Alumni Association, will preside

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, APRIL 17

FRIDAY APRIL 18

- *9-10-10 00 a m Studies in Histochemistry Dr Henry Bunting Joseph H Pratt Diagnostic Hospital
- *10 00 a m-12 00 m Medical Staff Rounds Peter Bent Brigham Hospital

MONDAY APRIL 21

- *12 15-1 15 p m Clinicopathological Conference Peter Bent Brigham Hospital

TUESDAY APRIL 22

- *12 15-1 15 p m Clinicoroentgenological Conference Peter Bent Brigham Hospital
- 5-00 p m Cutter Lecture Amphitheater Building D Harvard Medical School

WEDNESDAY, APRIL 23

- *9-10-10 00 a m Pediatric Clinicopathological Conference Drs James M Baty and H E MacMahon Joseph H Pratt Diagnostic Hospital
- *11-00 a m-12-00 m Medical Clinic Amphitheater Children's Hospital

(Notices continued on page xix)

used it successfully in the extraction of teeth and that he hoped Dr Warren might be willing to try it on a larger scale at the Hospital. Dr Warren finally consented,* and having made up his mind, did much as any of us would do today: he told his house-officer what was in the offing and suggested that he be on the lookout for a suitable case. This must be a patient requiring a relatively minor opera-

a pleasant diversity of talent and age so that conversation developing among them should be interesting. Of the medical men Dr Jackson was perhaps the first scientist of his day — a chemist, physicist, geologist and mineralogist, highly thought of by his contemporaries. Dr Gould was equally unusual, besides being a wise physician, he was well known as a conchologist and zoologist. One can



FIGURE 2 *The First Use in Boston of Ether as an Anesthetic Agent*
This half-tone illustrates the extraction performed on Mr. Frost and is reproduced from *Trials of a Public Benefactor*, by N. P. Rice (New York: Putney and Russell, 1858)

tion that should be sufficiently uncomfortable so that relief from pain through the use of Dr Morton's preparation — if this were possible — would be striking. And thereupon he turned his mind to more entertaining matters †

For some time Dr Warren had been considering the formation of a club where new ideas as they came along could be discussed intelligently by a representative group of men. At last he determined to hold a trial meeting of such a prospective organization and therefore invited to his house seven carefully selected friends: Messrs Abbott, Lawrence, Francis C. Gray, Theophilus Parsons, Martin Brimmer and George Darracott and Drs Charles T. Jackson and Augustus Gould. Like Warren himself, they were prominent in their various fields and interested in Boston and progress, and moreover, they included

judge, from its original composition, that the Thursday-Evening Club — as the organization came to be called — proposed to be no flippant affair but that its meetings were to be conducted with all possible seriousness and dignity.

In the meantime, on October 13, Gilbert Abbott, a twenty-year-old printer who had the misfortune of having a tumor on his neck, chanced to enter the hospital. Obviously, an operation would be to his benefit, and his seemed about the type of case that Dr Warren was on the lookout for. The upshot was that Dr Morton received the following letter:

Dear Sir, —

I write at the request of Dr J. C. Warren to invite you to be present on Friday morning, at ten o'clock, to administer to a patient then to be operated on, the preparation which you have invented to diminish the sensibility to pain.

Yours respectfully,

C. F. HAYWOOD

House Surgeon to the Massachusetts General Hospital

*Dr. Morton's advertisement in the *Transcript* for October 11 gives Dr. Warren's name as a reference. This suggests that Dr. Warren may have observed the new method in operation.

†The best accounts of Dr. Warren's part in the introduction of ether are found in the biography of Warren¹ and in his own article.²

terest of the surgeon as for the patient that the preparation should be administered for while it renders the latter insensible to the pain attending severe surgical operations, it affords the former the means of doing his work, freed from all interruptions on the part of the patient, and gives him facilities for performing operations in the most expeditious manner*.

Several apparently fortuitous incidents occurred during the interval between the appearance of these notices. Among others, Mr Tenney engaged in a new enterprise, Dr Bigelow began to explore a new field, and older men of great influence, like Dr Jacob Bigelow, Mr Edward Everett and Dr John C Warren, made their appearance on the scene. Dr Bigelow was president of the Massachusetts Medical Society, Mr Everett was president of Harvard

impressed by Dr Morton's methods that presently he signed an unusual contract† he agreed to study with Morton to master the art of dentistry and in return to be responsible for such advertising and other writing as his chief should direct. He proved an admirable publicity agent, so that in a surprisingly short time more than a hundred persons were able to testify that teeth could be extracted with negligible discomfort.

Young Dr Bigelow was deeply imbued with the numerical method of Louis as applied to clinical research and was bounding with energy and enthusiasm. He had been appointed to the staff of the Massachusetts General Hospital but so far had been given little opportunity to demonstrate his ability

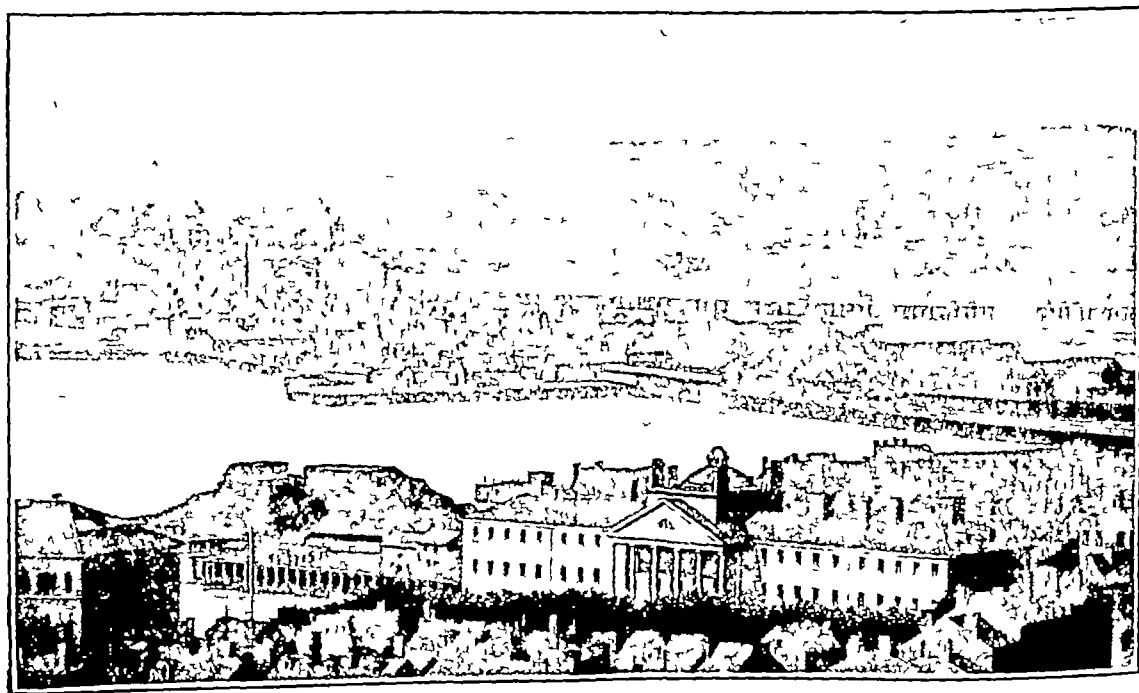


FIGURE 1 The Massachusetts General Hospital in 1846

The Ether Dome can be seen, as well as the new building of the Harvard Medical School, which is in the left foreground

College, and Dr Warren not only was senior surgeon at the Hospital and professor of surgery at Harvard Medical School but also had his finger in almost every pie important to the social and intellectual life of the city.

Mr Tenney, with a good newspaperman's sense of news values, had been present at Dr Morton's office to witness Mr Frost's extraction. He was so

*This is the first printed account giving any details of the operation. Its typographical errors make it all the more interesting. Dr George Hayward was the surgeon on the hospital staff next in seniority to Dr J. C. Warren. Dr Charles F. Heywood was the surgical intern. "The McLean wood" represents a reasonable cross between the two names. "The McLean Hospital" was probably meant to be printed. "the McLean Street Hospital" Mr Tenney probably wrote this note and Dr Gould was probably the respected physician referred to as being present. He lived across the street from Morton and was one of his friends.

When he read of Mr Frost's adventure, he perceived its implications and at once began to investigate it — first, by satisfying himself that Mr Frost had told the truth, and next, by making clinical observations in Dr Morton's office on the manner in which patients behaved after they had been put to sleep by the new process.

Soon the combination of Morton, Tenney and Bigelow was so well established that Morton considered himself justified in calling on Dr Warren. He stated that he believed that a means for preventing pain in surgical operations existed, that he had

†A copy of this contract is in the Boston Medical Library.

This was ether's coming-out party in Boston and the source from which Bostonians began to hear about it in an authoritative way

Dr Jacob Bigelow, besides being president of the Massachusetts Medical Society, was president of the American Academy of Arts and Sciences. The Academy was scheduled to hold a meeting on November 3, when Mr Benjamin Peirce, professor of astronomy at Harvard College, was to say something about a new planet that had been interesting Boston stargazers*. At the last moment he was unable to keep this engagement, and Dr Bigelow was compelled to find a substitute. It seemed natural to fill in with his son, who seemed to have something worth talking about. Unfortunately, there is no account of how his speech was received. The record states simply, "Dr Henry J Bigelow gave some account of a new process of inhalation employed by Dr Morton of Boston, to produce insensibility to pain during the performance of operation by the dentist and the surgeon." Yet the meeting had far-reaching results, it drew the attention of another group of influential people to ether particularly that of Mr Everett.

The new building of Harvard Medical School was to be opened the next day, and as part of the ceremonies Mr Everett had agreed to deliver an address. By way of preparation he admitted that he had done little more than glance over a copy of the history of the school and put together a few notes. When he heard young Bigelow at the Academy, however, he gathered that some sort of stupefying gas prepared by Dr Morton had been used with fair success to prevent pain in two surgical cases, and he was impressed with the youthful speaker's sincerity and ability. Therefore, apparently, he decided to make a graceful and noncommittal allusion to this in his speech, his words concerning the importance of training in relation to medical research are of special interest.

It is not to be expected that discoveries like Jenner's can frequently reward the investigations even of the most sagacious. To exterminate a disease which has desolated mankind for centuries, is of course an achievement not to be often repeated. But discoveries and improvements of all kinds are likely to keep pace with the advance of education in general and professional studies. The greater the number of individuals whose perceptive powers have been awakened and guided by sound studies and wise discipline, the greater the probability that some sharpened glance will penetrate the yet undiscovered mysteries of nature.

A few days later, young Dr Bigelow⁴ read his paper, "Insensibility during Surgical Operations Produced by Inhalation," before the Boston Society for Medical Improvement. This was an amplification of what he had said at the Academy so that one can judge why Mr Everett found his remarks noteworthy. Bigelow told of his experiments with ether, "the odor of which was readily recognized in the

preparation employed by Dr Morton." He reviewed the literature concerning its properties. He described Morton's technic for its administration and the way people reacted when they inhaled it. He stated that its use was clearly adapted to operations that were brief in duration, whatever their severity, he was less certain that it was applicable in operations requiring complete muscular relaxation, such as the reduction of dislocations and the repair of strangulated hernias, conceivably it might prove safe to administer for a long period and to produce prolonged narcotism.

The paper was printed as the leading article in the November 18 issue of the *Boston Medical and Surgical Journal* and was the first published description of the use of ether by any Boston physician.[†] But that particular date is worth remembering for another reason: it was the day on which Mr Everett's daughter developed a toothache. He took her to Dr Morton and described the visit in the following words:[‡]

She was thrown into a state of insensibility by breathing the vapour[§] of ether prepared in some undivulged way. The operation of inhaling the gas lasted about two minutes and the state of unconsciousness as much more. Some loss of time took place in consequence of her jaws being rigidly closed. The operation had to be repeated three times in consequence of the tooth breaking to pieces; and the process of digging out the roots would have been extremely painful if not performed in a state of unconsciousness. No unpleasant consequences of any kind followed the operation.

Mr Everett had been prevailed on to publish the address that he had delivered so offhandedly at the opening of the medical school. He decided to change the final proof, which was still before him, referring to the paragraph on medical research, he added the following footnote:

I am not sure that since these remarks were delivered a discovery has not been announced, which fully realizes the predictions of the text, — I allude to the discovery of a method of producing a state of temporary insensibility to pain, by the inhalation of a prepared vapor. A full account of this discovery is given in a paper, by Dr Henry J Bigelow, in the *Boston Medical and Surgical Journal*, for the 18th of November, 1846. Dr Bigelow ascribes its first suggestion to Dr Charles T Jackson, and its application under his advice, for the purpose of mitigating pain, to Dr W T G Morton, dentist, both of Boston.

I witnessed a very successful instance of the application of the prepared vapor, on the 18th of November, and was informed at that time by Dr Morton, that he had employed it in several hundred cases of dentistry. It has also been made use of with entire success at the Massachusetts General Hospital, and elsewhere in Boston, in capital operations of surgery. The few cases of failure may perhaps be ascribed to irregularities in the process of inhalation, or to peculiarities of temperament or constitution on the part of the patient.

I understand that great confidence is placed in this discovery, by the most distinguished members of the medical

*The *Boston Medical and Surgical Journal* for October 21, 1846 reported "Strange stories are told in the papers of a wonderful preparation in this city by administering which a patient is affected just long enough to undergo a surgical operation without pain." Apparently the editor Dr J V C Smith, took little stock in the early rumo's.

†This episode is described in Mr Everett's diary.

‡The spelling of "vapor" varies. Mr Everett spelt it "vapour" in his diary and "vapor" in his published address. Dr Jacob Bigelow in his letter to Dr Boott also used the former style.

§This information is found in Mr Everett's diary, deposited in the Massachusetts Historical Society.

And on October 16 Dr Warren made the following entry noted in his diary

In the morning went to the Medical College to make some experiments on the renovation of decayed bones

The second operation was performed on the following day and with more striking success. Thus, ether had begun to make a little noise around Boston when the Thursday-Evening Club convened

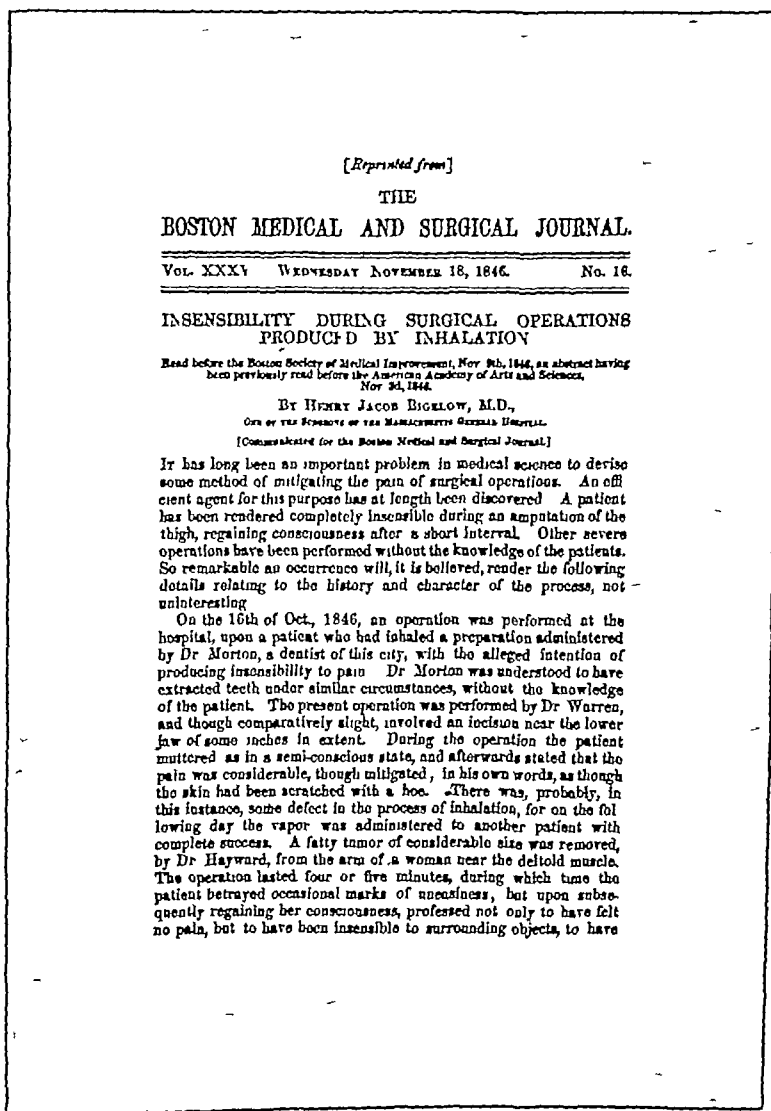


FIGURE 3 Title Page of a Reprint of Dr Henry J Bigelow's Paper

This is the first publication by a Boston physician describing the use of ether. The reprint is a curiosity because it is incomplete, all controversial discussions that appeared in the original paper having been deleted.

with glue. White glue gives, in some cases, a beautiful appearance, and the black gives great strength.

Did an interesting operation at the Hospital this morning, while the patient was under the influence of Dr Morton's preparation to prevent pain. The substance employed was sulphuric ether.*

*Both Dr Warren and Dr Hayward believed that the effect of ether in this case was incomplete; the suffering, however, was less than it would have been under ordinary circumstances, and the result was satisfactory enough to justify further trial. For Dr Hayward's recollection of this occasion see Hayward.²

for the first time on October 27, Dr Warren's record of this momentous occasion was as follows

At this meeting, the application of ether, for the prevention of pain in surgical operations, was first made the subject of discussion between Dr Gould, Dr C T Jackson, and myself, and we then learned from Dr Jackson, that he suggested to Dr Morton the use of ether for the prevention of pain in a patient who was to undergo a severe dental operation.

land by chance, because several isolated and inconsequential events in Boston combined to make many different persons of importance conscious of a great medical event, by friendship, because older men like Dr Jacob Bigelow, Dr Boott, Mr Everett and Dr J C Warren knew and trusted each other and were glad to lend their influence in promoting something of general usefulness that had been originated by younger colleagues

Ether reached France in a similar manner Dr John D Fisher,* an imaginative man who never followed the beaten track, had graduated from Harvard Medical School in 1825 He had gone abroad when he obtained his degree and had studied in Paris under Louis When he returned to Boston to practice, he took an active interest in progressive medicine, thinking especially of people less fortunate than himself He made several useful and original contributions among others, that of auscultation of the skull as a diagnostic method He is known most widely as founder of the Perkins Institution for the Blind Apparently, he did no formal teaching at the medical school, although in contemporary catalogues he is listed as "preceptor" — one of those practitioners who were chosen to be responsible for supervising both the professional studies and the moral characters of students placed in their charge

Francis Willis Fisher,† his nephew, was assigned to him in 1842, young Fisher was a mysterious person about whom little is known beyond the fact that he attended the Boston Latin School, took an active part in the affairs of the Boylston Medical Society as an undergraduate, joined the Massachusetts Medical Society as promptly as he could, and emulated his preceptor on graduation by going to Paris for final polishing

Dr John Fisher had been appointed to the staff of the hospital in 1846 and was interested in ether, he wrote to his nephew about it shortly after the second operation had been performed Francis‡ remarked that he would have been cautious in giving credence to the report he received had it reached him through the pages of a medical journal, coming to him from his former medical instructor, he could entertain no doubt of its truth He attempted at once, without success, to excite Velpeau and others of his surgical teachers to try it He next determined to etherize himself, before an appropriate audience, while he had a tooth pulled, this effort failed because he reached only the stage of excitement, and his obstreperousness was unpleasant Finally, in January, when Parisian doctors were beginning to receive English reports and to use ether with no great confidence, a Boston inhaler came to his hands complete with sponge and valves He demonstrated this to Roux and Velpeau, was invited by each of them to use the instrument in their clinics — which he

did with perfect success — and henceforward as he said with understandable complacency, the method took full possession of the French medical mind so that the inhalation of ether came to be employed in all surgical operations Friendship of a teacher for his student and the chance arrival of a Boston ether

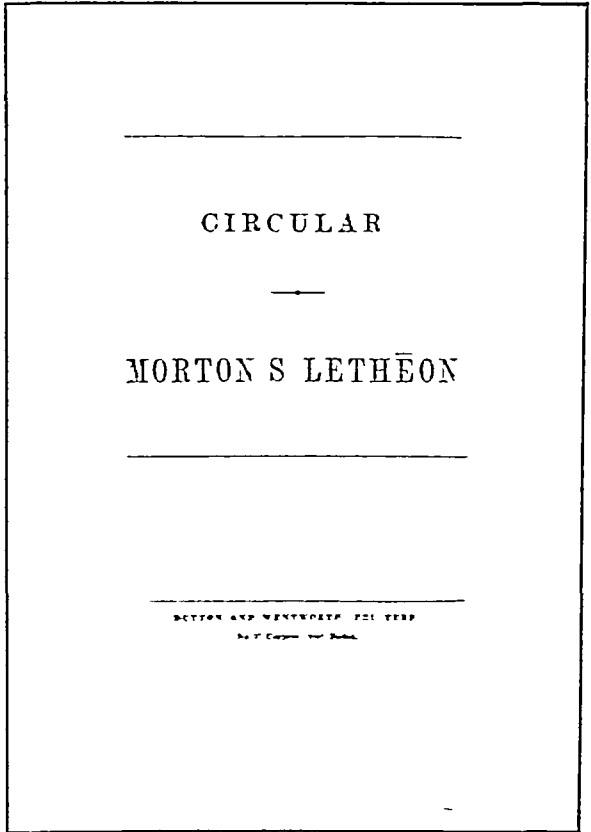


FIGURE 5 Title Page of the Third Issue of Morton's "Letheon" This probably appeared in December 1846 It is a bibliophilic rarity, since only three copies have been found one in the Arm Medical Library, one in the Treadwell Library, of the Massachusetts General Hospital and one among the Warren papers in the Harvard Medical School Library

inhaler in France at the moment it was needed seemed the most active catalysts there

Curiously, the introduction of ether into the medical practice of the United States proved more difficult There were at least three understandable reasons for this conservatism, distance between medical centers so that news traveled slowly and, above all, skepticism Morton and Tenney were eager to publicize their work and possibly their way of doing it failed to attain general approval They

*For a pleasant biography of Dr Fisher see Channing
†What little is known of Dr Francis Willis Fisher is found in the archives of the Harvard Medical School the records of the Boylston Medical Society and Harnington's History of the Harvard Medical School

‡A committee of the American Medical Association consisting of G. W. Norris and Isaac Parrish Philadelphia, John Watson New York City A. L. Pearson, Salem, and Hugh H. McGuire Winchester Virginia wrote an excellent account of the development of anesthesia. Dr Pearson was a pioneer in the use of ether, lost his life five years later returning from the New York meeting Shortly after passing Norwalk the railroad car in which he was sitting plunged through an open drawbridge into the water below

profession of this vicinity, and that they are disposed to regard it as an effectual method of inducing complete insensibility under the most cruel operations, by means easily applied, entirely controllable, and productive of no subsequent bad consequences. It seems not easy to overrate the importance of such a discovery.

A Cunard mail steamer was due to sail for England about the first of December. Among a cargo of

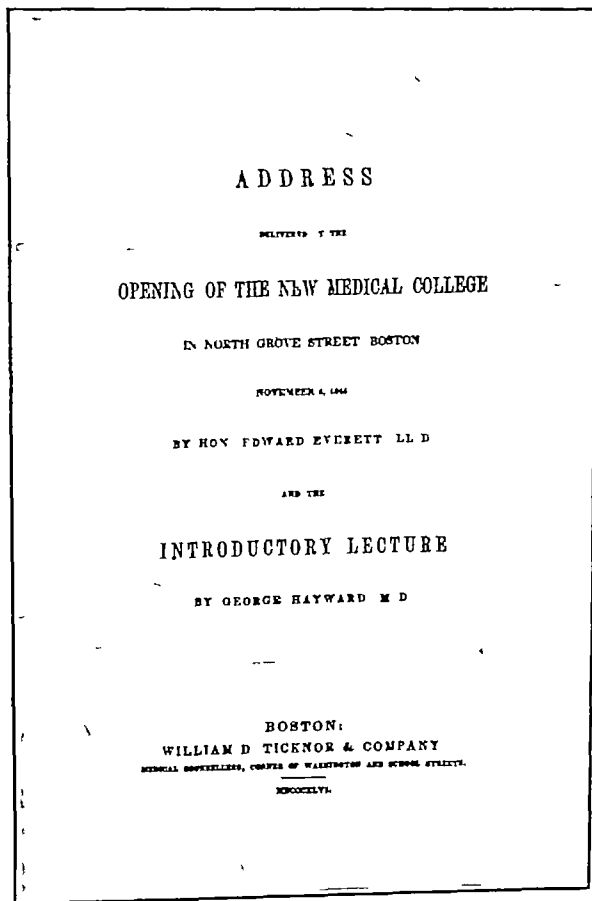


FIGURE 4 Title Page of Mr. Everett's Address

According to the Boston Medical and Surgical Journal, the address was clothed in beautiful language and was much admired for its elevated sentiments and elegance of expression. Mr. Everett believed that it was the first nonprofessional publication in which the use of ether was mentioned. The address was printed at the request of the students at the Harvard Medical School, and is misdated, presumably owing to their inexperience in proofreading.

other valuables, she carried copies of Mr. Everett's address and of Dr. Bigelow's paper, as well as letters describing the use of ether from Mr. Everett, Dr. Jacob Bigelow and Dr. Warren to sundry people of influence in Great Britain and France.

Dr. Francis Boott,* an Englishman who graduated from Harvard College in 1810, was a contemporary

*A sympathetic biography of Dr. Boott is found in the Harvard Archives Widener Library reprinted from *The Gardener's Chronicle* 1864.

and friend of Dr. Jacob Bigelow and Mr. Everett. After finishing college he returned to England, obtaining his medical education in Edinburgh. He practiced for a few years in London but soon inherited money enough so that he could do as he pleased. He retired from practice and took up botany as a hobby, but kept his hand on medical politics in general, particularly as they concerned University College, where he had taught and where he continued to serve on the Council. He had a talent for friendship, he had traveled across the Atlantic often enough so that he was in constant touch with Cambridge and Boston contemporaries.

The American mail arrived about the middle of December, and Dr. Boott† opened a letter from his friend Jacob Bigelow with usual relish and studied its contents with particular care. The letter read as follows:

November 28, 1846

Boston

My dear Boott:

I send you an account of a new anodyne process lately introduced here, which promises to be one of the important discoveries of the present age. It has rendered many patients insensible to pain during surgical operations and other causes of suffering. Limbs and breasts have been amputated, arteries tied, tumors extirpated, and many hundreds of teeth extracted without any consciousness of the least pain on the part of the patient.

The inventor is Dr. Morton, a dentist of this city, and the process consists of the inhalation of the vapour of ether to the point of intoxication. I send you the *Boston Daily Advertiser*,‡ which contains an article written by my son Henry, and which is extracted from a medical journal, relating to the discovery.

Let me give you an example. I took my daughter Mary, last week, to Dr. Morton's rooms to have a tooth extracted. She inhaled the ether about one minute, and fell asleep instantly in the chair. A molar tooth was then extracted, without the slightest movement of muscle or fibre. In another minute she awoke, smiled, said the tooth was not out, had felt no pain, nor had the slightest knowledge of the extraction. It was an entire illusion.

The newspaper will give you the details up to the date, since which other operations have been performed with uniform success.

Since college days Dr. Boott had known that anything Dr. Bigelow said was always true. On the morning after he had received the letter he got hold of some ether, Miss Lansdale, who had a molar tooth of which she wished to be rid, and Dr. Robinson, a dental surgeon, in the presence of Mrs. Boott and his two daughters, he etherized the lady and watched Dr. Robinson extract her tooth, painlessly and without difficulty. He then reported the matter to his friend Robert Liston, who, in turn, realizing that anything Dr. Boott said was true, immediately used ether at the University College Hospital in a case of thigh amputation and in a case requiring removal of the great-toenail, in both cases with excellent results.

I believe that this account outlines the pathway through which the discovery of ether reached Eng-

†From a description of this event it is clear that Dr. Boott was one of those who received a copy of Mr. Everett's address.

‡The *Boston Daily Advertiser* for November 19 reprinted Dr. Bigelow's article in full. This is the first complete and contemporaneous reprint with which I am familiar. The *Lancet* for January 2 1847 reprinted the *Boston Daily Advertiser's* reprint.

THE HOSPITAL — A LOOK AHEAD*

Some Aspects of Clinical Investigation

GEORGE R. MINOT, M.D.†

BOSTON

CLINICAL investigation has been conducted in the Massachusetts General Hospital with ever-increasing frequency and significance. In the future the hospital will continue to be a leader in such work, which will be developed more than ever before. From research of today come new forms of treatment tomorrow. It is treatment that patients are particularly concerned about. The physician, by investigative means, learns much about the etiology and diagnosis of disease, and investigative studies give information of a wide sort to the physician and the scientist.

This type of work is often done in conjunction with medical schools, but the work is frequently done entirely at the hospital by clinicians. Research of the clinical sort begins at the bedside. The needs of the patient urge the physician to make his scientific inquiries. Indeed, it may be said that research begins in the library, for the literature must be explored to determine what has already been accomplished. A good working library like the Treadwell Library is of great value to the hospital, but the members of the hospital must also make use of such libraries as the Harvard Medical School Library and the Boston Medical Library, where many books and scientific journals are at hand.

A clinical investigator cannot be defined by a rule of thumb. He must be an able clinician and one with wide interests who understands human beings and can act wisely for all the multiple aspects of a given patient. He must have an ardent desire to seek knowledge by scientific methods, as well as a wish to advance knowledge so that succeeding investigators will find the results nearer the ultimate goal.

Descriptions of previously unrecognized conditions often depend on the observation of several cases and not on planned investigation. The collection of proper information over long periods to formulate knowledge about prognosis, which in many chronic conditions is imperfect, represents a simple type of investigation. There is need for more accurate work of this sort. The question of the origin or cause of disease is of particular importance

to the clinical investigator and may require intricate and complicated studies.

The clinical investigator can study the problem by various methods at his command and with the aid of laboratories of various sorts. The search for truth regarding the laws of Nature is fundamental. One of the things that may be of great advantage in future investigation is co-operation among physicians, scientists and all types of scholars trained in different ways and at different sorts of institutions. Such co-operation, when spontaneous, is fruitful, but when compulsory, may be sterile.

This hospital will become even more of an educational center to train young men to be all types of physicians and surgeons. Among these men are future general practitioners. Such persons will always be of great value to the community and deserve to be looked up to.

The hospital will, of course, always continue to take care of patients and will investigate disease with increasing frequency, and although today it may be regarded as a consulting center, in the future it will certainly be considered a vital consulting center. The hospital is not competing with doctors, it is indeed helping them.

One must expect more full-time men at work at this hospital. I emphatically do not mean men who are not permitted to see private patients.

The importance of public education has been growing, and the hospital may be expected to take a leading part in such work. A preventive-medicine clinic is something we may expect. Preventive work has a broad conception — it must include all activities to increase health. Doctors must plan to construct as well as to reconstruct health. When the patient reports to the Out Patient Department in the future, he may even ask to go to the preventive-medicine clinic, and the public must be trained to appreciate the significance of preventive medicine, so that people will voluntarily go to such a clinic.

A growing understanding of the numerous factors that cause disease will determine in part the future course of preventive medicine. There is the prevention of disease and of health depreciation by the attainment of better general health. The chief objectives of preventive medicine have been to reduce things harmful in the environment and to increase the body's immunity.

The control of infectious diseases is increasing, and yet devastating epidemics occur. Chronic progressive diseases characteristically frequent in the

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 †Presented at a symposium "The Hospital in the Community" held during the Esther Dyer Centenary of the Massachusetts General Hospital, Boston, October 16, 1946.
 Professor of medicine, Harvard Medical School; director, Thorndike Memorial Laboratory, Boston City Hospital; visiting physician, Boston City Hospital; member, Board of Consultation, Massachusetts General Hospital.

kept track of the literature on the use of ether as it accumulated and issued informative circulars from time to time in the form of a small pamphlet entitled "Letheon." The various issues of this unusual publication were more or less like present-day commercial advertisements and had little effect. The *Boston Medical and Surgical Journal* printed more serious articles, but these reached few physicians south of Massachusetts. By degrees, however, the fame of ether after its trip abroad came back to the United States through British and French medical journals. With human perversity physicians on this side of the Atlantic seemed willing to accept a procedure advocated in Boston only when it had the stamp of foreign approval. The New York Hospital began to use ether in the early spring of 1847, and a little later, surgeons at the University of Pennsylvania and the Jefferson Medical College took it up. By 1848, when the American Medical Association met, ether had come into its own over the entire world.

* * *

To my mind, this curious cycle of episodes is worth remembering. Chance played a large part in making the Ether Dome as famous as it is. If Mr. Tenney had happened to be a less aggressive reporter, if the Thursday-Evening Club had not held its first meeting when it did, if Professor Peirce had been able to fill his engagement to speak at the meeting of the Academy, if Mr. Everett's daughter had developed her toothache a few days earlier, if Dr. Boott had gone to college in Cambridge, England, instead of in Cambridge, Massachusetts, or if Francis Fisher had been assigned to another preceptor than his uncle, the whole story of ether might have been dif-

ferent. And without friendship — Mr. Tenney's friendship for Dr. Morton, Dr. Warren's friendship for the Bigelows, Dr. Jacob Bigelow's friendship for Dr. Boott, Dr. Boott's friendship for Robert Liston, and Dr. Fisher's friendship for the Hospital and his nephew — Mr. Eben Frost's toothache might have been of no great interest to anyone but himself, and the first use in Boston of ether as an anesthetic agent might have been insignificant.

Even in these days when science has complicated practice and research is so complex, it may be well to keep in mind the importance of two such simple imponderables as chance and friendship. Chance will always play an unpredictable part in shaping new ideas, medical investigators must not be led astray by the lure of intricate machinery but must ever be alert to use their eyes to see unexpected, apparently insignificant occurrences that may later prove to be great events. Friendship will always be necessary to our art so that as many people as possible may work together to develop its future for the greatest common good.

REFERENCES

- 1 Warren E. *The Life of John Collins Warren M.D.* 2 vol. Boston Ticknor and Fields 1862.
- 2 Warren J. C. Inhalation of ethereal vapor for prevention of pain in surgical operations. *Boston M & S J* 35 375 379, 1846.
- 3 Hayward, G. Some account of first use of sulphuric ether by inhalation in surgical practice. *Boston M & S J* 36 229 234 1847.
- 4 Bigelow H. J. Insensibility during surgical operations produced by inhalation. *Boston M & S J* 35 309 317 1846.
- 5 Boott F. Surgical operations performed during insensibility produced by inhalation of sulphuric ether. *Lancet* 1 5-8 1847.
- 6 Channing W. John D. Fisher M.D. *Boston M & S J* 42 117 121, 1850.
- 7 Fisher, F. W. Ether inhalation in Paris. *Boston M & S J* 36 109-113 1847.
- 8 Norris G. W. Parrish I., Watson, J., Pearson, A. L., and McGuire, H. H. Anesthetic agents. *Tr A M A* 1 176-196 1848.

proteins and fruit. These foods are not luxuries but necessities.

Elvehjem³ has noted that diets containing 9 per cent of casein produce good growth but that when 6 per cent gelatin is added, poor growth results. Tryptophan or protein low in tryptophan or nicotinic acid counteracts this retardation. Thus, poor-quality proteins may in the future be regarded as more harmful than a diet low in protein.

The methods used in the diagnosis of subclinical deficiencies in human beings obviously need new and improved chemical measurements. Mild deficiencies are not obvious, and may be difficult to detect. Tests of various kinds will be improved and developed to aid in the understanding of such conditions. Hyperthyroidism, tuberculosis, pregnancy and the like may increase the need for certain dietary factors and may lead to suboptimal nutrition. Nutritional deficiency in man is of a multiple nature.

The relation of nutrition to dental caries needs much study. Dental caries is the most widespread nutritional defect, one or more nutritional factors involved may be harmful, or the lack of a factor or factors may be causative. Diets high in fermentable sugar may induce dental caries, and increased intakes of fat and protein minimize dental caries. The relation of nutrition to resistance to diseases and to infectious processes also needs further study.

The essential trace elements, such as cobalt and zinc, that occur in living matter but whose importance is unknown stand as a challenge to physiologists and nutritionists. It is recognized, however, that men working in cobalt (radioactive) and pitch-blend mines frequently develop bronchiogenic carcinoma.

One must recognize such work as that of Rhoads,⁴ in which indol causes no anemia in dogs with proper diets but induces severe anemia when the animals are given black-tongue diets. Butter yellow is tolerated by normal animals, but if the vitamin B complex level is low, cancer develops. Rhoads has also shown that dietary constituents such as riboflavin and casein protect animals against the carcinogenic effects of butter yellow (*p*-dimethylaminoazobenzene).

Cancer research is a great responsibility that confronts scientific medicine. Cancer is a disease predominant in the later decades of life. There has been great improvement in the methods of diagnosis and treatment of internal cancer, and yet the death rate per million population has been increasing. People must learn to seek competent medical advice when an early suspicious sign or any abnormality that might predispose to the disease is noticed. Prompt and effective treatment for cancer is essential.

There is often no indication of why a cancer develops. Occasionally, the occurrence of chronic irritation of potential tumor sites is well recognized,

as in the mouths of tobacco chewers. Cancer may involve almost any part of the body, but the digestive tract is usually affected.

One of the causes for the neoplastic state seems to be viruses.⁵ Some of the viruses are products of disordered cell metabolism, and others are living entities. Tumors induced in mice by methyl cholanthrene are not influenced as those resulting from butter yellow are by the addition of one or more substances of a similar sort in the diet. In such cases it does not seem that living viruses play a role. The high incidence of liver cancer and cirrhosis in the African Bantus and the poor diet consumed by these people suggest a causal relation. Whatever the cause of cancer may be, a great many studies are needed to determine clearly the fundamental aspects.

Disorders of the blood must not be forgotten in clinical investigative studies. Leukemia is considered by some to be comparable to cancer. No one has ever recovered from this disease, but x-ray and allied therapy is palliative. Chemotherapy may offer some hope. Investigators would like to identify a specific component of the cancer cell and of the leukemic cell. Indeed, what is the difference between a leukemic and a normal cell? For some mysterious reason the blood cells in leukemia grow in a purposeless manner. A radioactive atom might be incorporated in a leukemic cell, in the hope that in some manner leukemia would be vanquished.

Certain anemias also need elucidation. The first evidence that there are two distinctive components of liver extract effective in nutritional macrocytic anemias came from the observations of Wills⁶ on monkeys. In these animals, in which anemia had been produced by the feeding of a defective diet similar to that of patients with tropical macrocytic anemia of pregnancy in India, a highly purified liver extract effective in pernicious anemia was found to be ineffective. This finding led to a similar demonstration of the inefficacy of purified liver extract in human patients. The cases in this group include certain patients with macrocytic anemias of the tropics and of pregnancy, as well as so-called "refractory anemias" with megaloblastic bone marrow. Watson and Castle⁷ have studied this problem. Whether such patients require the active principle of liver extract that is effective in pernicious anemia, as well as an additional factor present in less refined liver extract or only the latter material, is unknown. As yet, it has not been determined whether folic acid, present in only trivial amounts in liver extract, is as effective in these cases as it is in pernicious anemia.

Rheumatoid arthritis is being studied expertly here by Dr. Bauer and his associates. The nature and course of this disease necessitate a detailed clinical and laboratory study over a long period. Rheumatoid arthritis is a disease of young adults and often continues throughout life. It is more

later years of life will continue to assume greater and greater significance. Infections of childhood will become rarer perhaps because of better control and better treatment. It may even be supposed that cancer could be controlled by the injection of some mysterious chemical comparable to insulin in diabetes mellitus or penicillin in pneumococcal pneumonia.

The degenerative diseases such as those with high blood pressure will constitute an ever-increasing threat to national health. To be sure, these diseases have occurred for many thousand years, but their social importance is new. There is now a rapidly increasing number of elderly people, who are presenting new problems. The hospital will concentrate more and more on problems of health in later years of life, but will continue to attack diseases frequent in youth.

Effective prevention is usually possible only when the whole history of causation is known. The etiology must often be considered to include multiple causative influences.

Personal preventive medicine supplements public-health efforts. The early discovery of a disorder that will be more frequent in the future will allow the maximum benefit from therapy. Comprehensive periodic health consultations are essential—not a purely routine physical examination but a study that comprises a detailed history and complete consideration of the patient as a person, including the analysis of such habits of living as diet, rest and work. Thoroughness and individualization will always be needed.

Education in health for all age groups and by every means available will be an increasingly important medical problem. Sensationalism must be avoided. "The future of preventive medicine is bright whatever its precise course may be," Sleghtitz¹ said, adding "Medical science can give health to no one, but it is daily becoming more competent in guiding those who wish to *earn* health." Good health can be bettered, and man made to live longer, these are among the effects of the prevention of actual disease.

There are types of clinical investigation that demand organized study by institutions so that data can become available over many years and generations before final analysis is made—for example, creative work to determine the exact qualitative and quantitative influence, on thought and social life, of dietary factors alone or in combination and under varying climatic environments. The history of the people of the world could perhaps be written in terms of diet, as Zinsser² has done in terms of epidemics. Initiative, progress, success and the happiness of a people tend to go hand in hand with an abundance of food and a good diet.

Adequate and good food is fundamental to health. The most fertile field in the world of medical research today is nutrition. Nutritional, especially

vitamin, deficiency leads to ill health and distinctive diseases. Niacin, for instance, prevents pellagra, but mild deficiency of various vitamins may lead to chronic malnutrition, although the patient may take a sufficient number of calories not to lose weight. Nutritional studies regarding the lack of food elements, the faulty distribution of food and the great value of proper food for children must in future be a primary concern.

It is quite possible that more vitamins will be identified. Little is known regarding the taste appeal of foods, and information of this sort lies ahead. I wonder why some people really like liver and others dislike it. Others object to kidneys or oysters, whereas some think they are delicious.

The composition of foods should be known. Such studies may relate to enzymes and their mechanisms, which are not familiar subjects at present. Much lactose in the diet may increase the synthesis of riboflavin, but it may decrease that of other factors. Fat may reduce the production of riboflavin in the gastrointestinal tract. Natural diets may give effects distinctly different from those of synthetic diets, but it is the natural diet that man uses. The world is full of food potentialities, and the anticipated demands for foods of superior nutritive quality need re-evaluation.

An adequate dietary history is difficult to obtain, and yet it reveals a great deal about the nutrition of the patient. In the future, customs may change as they have in the past hundred years—fresh fruit is vastly more frequent, today, and red meat is rarer. Greater attention should be paid to dietary histories and to the importance of the effects of foods. One cannot feed by pure chemistry—the diet may be varied and yet deficient. A patient may be ashamed to admit that his diet is poor. This may be due to eccentricity, lack of teeth or ignorance, and the role that such difficulties play must be appreciated.

One must distinguish between what the community has to eat and what the individual has. The patient may be a fussy, finicky eater and may say about certain foods if the question is brought up, "The family have them but I do not eat them." Indeed, social adjustments may be vital before the correct food has been obtained or digested. It should be remembered that to order a diet is one thing but to cure a patient is another. A proper diet of natural foodstuffs is all that is necessary for prevention of disease caused by faulty nutrition.

It must also be realized that little is known about optimal nutrition as opposed to usual nutrition. The former should be the goal—not merely adequate nutrition.

Rising income is associated with increased consumption of milk, fruit, eggs, vegetables and meat and with better growth in children and improved general health. Such foods are the protective foods—the ones rich in vitamins, minerals and first-class

proteins and fruit. These foods are not luxuries but necessities.

Elvehjem² has noted that diets containing 9 per cent of casein produce good growth but that when 6 per cent gelatin is added, poor growth results. Tryptophan or protein low in tryptophan or nicotinic acid counteracts this retardation. Thus poor-quality proteins may in the future be regarded as more harmful than a diet low in protein.

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frequent in women than in men and more prevalent among the poor. It may begin insidiously or abruptly. Symptoms may disappear for several years, but recurrence is the rule. States of anxiety may precipitate an attack. The patients are apt to suffer from mental depression. This disease is of national importance because, although seldom fatal, it cripples many.

The factors regulating effusions in rheumatoid arthritis and those regulating the rate of formation and composition of synovial fluid are little known. Studies on mucin, which is obviously involved in rheumatoid arthritis, are needed. Ascorbic acid may play a role in the destruction of mucin. Greater knowledge should be acquired regarding the pathogenesis of the subcutaneous nodules characteristic of the disease. Studies of this sort as well as the psychiatric aspects of patients with arthritis—indeed, matters pertaining to all aspects of the disease—demand investigation.

Physics will concern investigators much more than in the past. Physicists and other natural scientists may even aid in the study of medicosocial problems. The electron microscope gives information about viruses and the diseases they cause. It can scarcely be foretold what will be discovered concerning the origin of living matter.

* * *

Many diseases and problems besides those mentioned will be studied at this hospital, and undoubtedly great progress will be made under the able leadership of Dr. J. H. Means and his successors. One can never tell when the cure for some dread disease is right around the corner.

The public must be educated to look on research as an essential activity and to understand the practical application and the enormous cost of undertaking investigation. No member of a community passes through life without receiving directly or indirectly the benefits of research done in such a great hospital as this. We all owe much to the Massachusetts General Hospital.

REFERENCES

1. Stieglitz, E. J. *A Future for Preventive Medicine*. 77 pp. New York Commonwealth Fund, 1945. P. 68.
2. Zinsser, H. *Rats, Lice and History*. 301 pp. Boston: Little Brown & Company, 1935.
3. Elvehjem, C. A. Future studies in nutrition. *Nutrition Rev.* 4:1-6, 1946.
4. Rhoads, C. P. and Miller, D. K. Induced susceptibility of blood to indole. *J. Exper. Med.* 67:273-297, 1938.
5. Rous, P. Cancer problem. *American Scientist* 34:329-358, 1946.
6. Wills, L., Clutterbuck, P. W. and Evans, B. D. F. New factor in production and cure of macrocytic anaemias and its relation to other haemopoietic principles curative in pernicious anaemia. *Biochem. J.* 31:2136-2147, 1937.
7. Watson, J., and Castle, W. B. Nutritional macrocytic anemia, especially in pregnancy: response to substance in liver other than that effective in pernicious anemia. *Am. J. M. Sc.* 211:513-530, 1946.

ATELECTASIS AS A FACTOR IN THE MEDICAL TREATMENT OF PLEURAL EMPYEMA THE NECESSITY OF COMBATING ATELECTASIS BY REMEDIAL BREATHING EXERCISES

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THE therapeutic management of empyema of the pleura has been revised because of the recent favorable experiences with penicillin. The treatment by open drainage after rib resection has been the generally accepted procedure in adults in practically all cases except those due to tuberculosis, actinomycosis and malignant neoplasm; this approach was based on the experiences in World War I and the report of the American Empyema Commission (1918), which clarified the rules for correct timing. Since then chronic empyemas have been seen less often than formerly.

Chronic empyemas are usually grouped in two categories: cases in which the original condition has never been recognized and a collection of pus has remained after the disease had been overcome by the body, and those in which the condition is a sequel of an acute empyema treated in the conventional way with the effect of overcoming the disease but without effecting the complete evacuation or

resorption of the pus. The unsatisfactory results in this group are usually due to too early removal of the drainage tube, to an improperly placed opening so that a pool of pus remains at the bottom of the pleural cavity, to encapsulated pockets or to a foreign body—usually a tube—in the empyema cavity. In both groups, those with and without surgical treatment, the persistent empyema may be maintained by incomplete expansion of the lung, owing to a bronchopleural fistula, thickening of the pulmonary pleura and atelectatic fibrosis of the lung. In pleural exudates and empyemas, fibrin is deposited on the pleura in varying amounts. The usual roentgenologic terminology is inaccurate in that the deposits are often described as thickened pleura. In the early stages these masses of soft-tissue density represent nonorganized fibrin deposits that undergo later organization through the ingrowth of capillaries from the underlying pleura. Thus, the roentgenologic term is meant to comprise both conditions, since there is no way of distinguishing the nonorganized layer of fibrin deposit, still

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capable of being resorbed, from the final organized product, which represents pathologically thickened pleura

It has been shown, clinically and experimentally, that the parietal and the pulmonary pleuras behave in a different manner in pleural inflammations, whether they are pneumococcal or tuberculous, serofibrinous or purulent.^{1,2} In the majority of cases, whereas thick layers of the deposits are found

pleural effusion begins to be resorbed, the obstructive atelectatic areas resist more obstinately the expanding traction because the factors causing the obstruction, such as kinks of the bronchi and accumulated secretion, are apt to persist. The presence of obstructive atelectasis, even if local and patchy, counteracts the tendency toward re-expansion. As a consequence of the collapse, the moist surfaces of capillary bronchioles come in contact with each

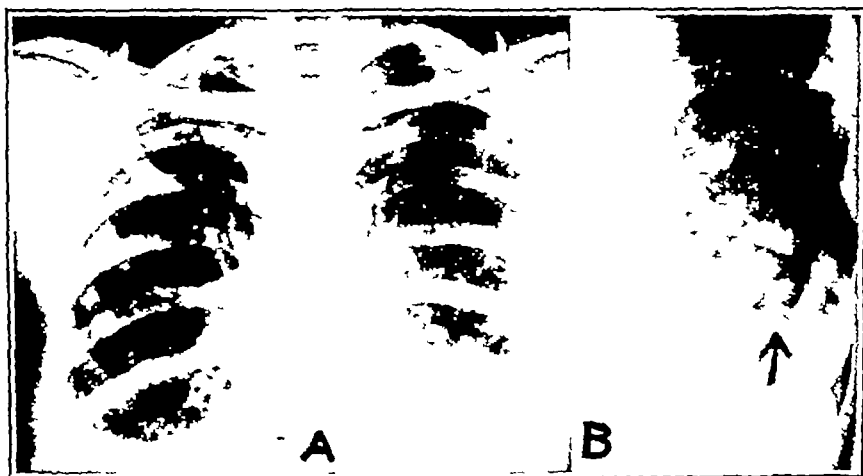


FIGURE 1 Pleural Effusion before (A) and after (B) Thoracocentesis
Note the plate-shaped area of obstructive atelectasis (arrow) in the latter roentgenogram

along the chest wall, only thin deposits or none at all are observed on the visceral pleura. This does not hold true for the posthemothoracic empyemas that develop after blood coagulums have been laid down more or less uniformly. A somewhat different behavior of the pleural surfaces, however, is recognizable even in such cases. As pointed out by Samson et al:³ "For some reason as yet unexplained, the peel over the parietal pleura is always thicker than that on the visceral pleura." The thinness of the deposits on the pulmonary pleura suggests that thickening of the pleura probably plays a minor role in the maintenance of the collapsed state of the lung in the usual nonhemothoracic empyema. It appears that, in the majority of cases, atelectasis is more important in hampering the re-expansion of the lung.

According to the textbooks, the atelectasis occurring with pleural effusion is of the compression type. The extrinsic pressure squeezes all the air from the alveolar sacs until they collapse and the capillary bronchioles also collapse. The matter, however, is not so simple as that. There is ample evidence from pathological and roentgenologic observations that, in addition to compression atelectasis, obstructive atelectatic processes in varying degrees occur. Although the compressed lung should respond readily to the expanding pull as soon as the

other, and great force is needed to overcome the surface tension to separate them again.

Pathological evidence of obstructive atelectasis with pleural effusions has seldom been described, although it is easily observed. At autopsy in cases with moderate pleural effusion, the atelectatic portions of the lung are identified by the depression of the surface, dark color and firmness. Quite often, the borderline toward the aerated area coincides with the pattern of the interlobular septums on the lung surface, moreover, isolated or multiple lobules, which are elevated, pale and air filled in the midst of otherwise atelectatic areas, are observed and on the other hand, beyond the compact atelectatic zone, isolated atelectatic lobules, depressed, dark red and firm in the midst of a well aerated section, frequently occur. When atelectatic areas are cut through, the surface exposed is not dry and gray as would be expected in compression atelectasis but dark red and moist, with much fluid oozing out, thereby showing the picture of obstructive or resorption atelectasis. In other cases the edge or even larger portions of the middle and lower lobes have been turned up, owing to the buoyancy of the lung floating in the fluid. Sometimes such a turned-up edge is found to be fixed by recently formed adhesions, which prevent the restoration of the normal position, the linked bronchi do not straighten

out, and the parenchyma served by them remains in its atelectatic condition. These observations on the gross morphologic appearance of the lung in pleural effusion show that, in addition to compression, obstructive atelectasis—due to collapse and kinking of bronchi and to retention of secretion in

lung. If the lung persists in its atelectatic condition for a longer time, however, it is apt to suffer irreparable alterations. Pleurisy is not restricted to the superficial layers of the pulmonary pleura. In chronic empyema the inflammation extends into the superficial interlobular septums and deeper,

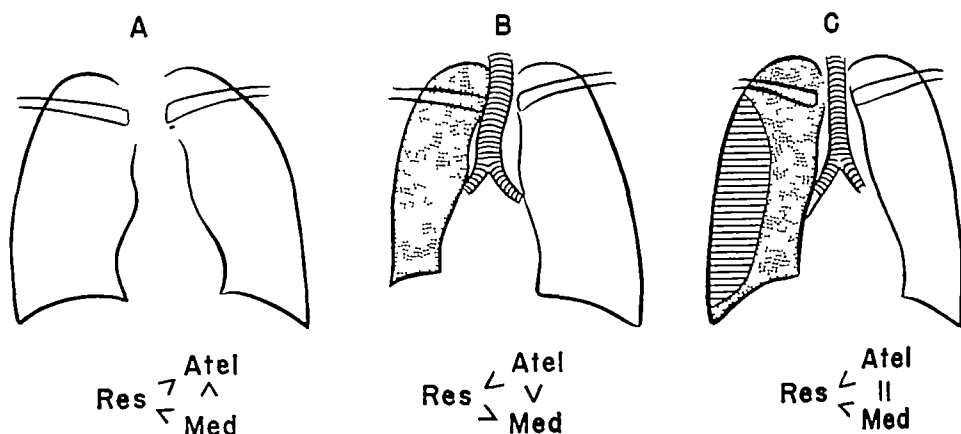


FIGURE 2 Diagram Illustrating Three Possible Events in the Course of Pleural Effusion without and with Persistent Atelectasis

Res = resorbing pull, Atel = atelectatic resistance of the lung against its re-expansion, Med = rigidity of the mediastinum resisting lateral shift

In A, the resorbing pull is large, and the mediastinum is stable. The atelectatic lung is easily re-aerated, and complete recovery results.

In B, the atelectasis is rigidly maintained, the resorbing pull is strong and the mediastinum is movable. Resorption of the exudate, persistent atelectasis and deformity of the chest result.

In C, the atelectasis is rigidly maintained, and the mediastinum is immobile, a residual empyema pocket and atelectatic induration of the lung result.

the poorly ventilated dependent portions of the lung—occurs.

Roentgenologic observations also confirm the presence of obstructive atelectasis in pleural effusion. More extensive collapse of one lobe or lobar segment, as well as unusual arrangement of the pleural fluid in the absence of pleural synechia, is analogous in appearance and origin to the selective collapse in pneumothorax and is due to obstructive atelectasis. If the mediastinum is pulled to the side of the effusion during the period of resorption or following a thoracentesis, the presence of obstructive atelectasis is indicated. Furthermore, I have observed plate-shaped areas of obstructive atelectasis immediately after thoracentesis (Fig. 1).

The functional aspect of these facts has recently been confirmed. In an analysis of the effects of pleural effusion on respiration, Altschule and Zamcheck⁴ showed that the functional reserve (supplemental) air, as well as the complementary air, increases only moderately eighteen hours after thoracentesis. Restoration of the vital capacity to its normal value takes about a month, indicating that great resistance must be overcome to reventilate the atelectatic lung.

This is the situation so long as no irreparable pathologic changes have occurred in the collapsed

larger interstices. Lindblom⁵ summarized his careful studies by pointing out that the longer the duration and the greater the purulence of a pleural effusion, the more extensive the pleurogenic interstitial pneumonia and the resulting fibrosis.

Atelectasis persisting for a long period, even without supervening inflammation, may in itself incite fibrosis of the lung. It has been shown that the occasional edema of the interstices may persist for a long time, resulting in fibrosis. In this way the interlobar septums and the perivascular and peribronchial interstices are widened. The involved area of the lung loses its plasticity and becomes more rigid.⁶ Residual or supervening infection in the lung or bronchi may add to the permanent loss of elasticity of the involved portion of the pulmonary tissue.

All these developments initiated by long persistent atelectasis have a crippling effect on the lung; moreover, they prevent the re-expansion, adequate diminution of the residual empyema cavity and final resorption of the empyema.

The aim of the treatment of pleural empyema is twofold: to combat the inflammatory disease with all its complications and to rehabilitate the lung. The classic surgical procedure combined with supportive medical treatment is directed at both aims.

Purely medical treatment with bacteriostatic or antibiotic drugs may stop the activity of the disease, and the body may or may not successfully handle the residual empyema. The problem of residual empyema similarly exists if the pleural taps are not continued with enough frequency, or if it is impossible to withdraw the fluid further, because it becomes inspissated or encapsulated in pockets

means, mobilized by the body to resorb the residual empyema, must overcome the tendency of the lung to maintain its collapsed condition. Since this resorption occurs in a relatively rigid cavity, the thoracic cage, a considerable pull must be exerted on the lung, for the present purpose, this may be called the "resorbing pull." The increased intrinsic resistance of the lung to re-expansion was briefly

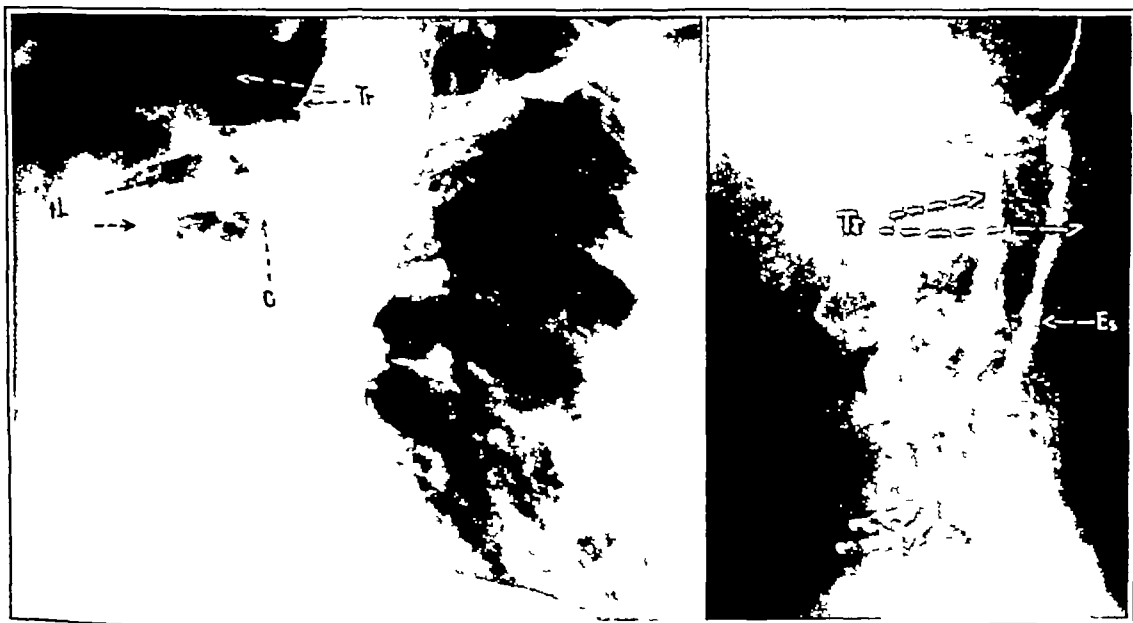


FIGURE 3 Case 1

The roentgenogram on the left shows postpleuritic contraction of the right lung (Tr = trachea, C = carina, L = border of the left lung herniated into the right half of the chest). The x-ray film on the right is a bronchogram of the right half of the chest, revealing obliteration of most of the smaller bronchi and bronchiectasis of the few patent ones (Tr = trachea, Es = esophagus).

that cannot be reached with the needle. I have recently seen a series of chest roentgenograms in such cases in which residual pockets of retained empyema, thickening of the pleura and deformation of the chest resulted from penicillin treatment without or with insufficient evacuation of the empyema.

A knowledge of the mechanical forces involved is essential to a better understanding of the occurrence of residual empyemas and to the planning of support for the body in its endeavor to resorb the fluid.

There have always been cases of pleural empyema in which the disease subsided and healed in spite of conservative treatment, incomplete surgery or no therapy. Some healed with few sequelae, others with permanent damage to the underlying lung, others with residual chronic empyemas, and still others with gross chest deformities; there were often combinations of all these sequelae.

There are basically three forces that in combination, control the rate of resorption of pleural effusions. The structural, physical and biochemical

mentioned above. For simplicity, the factors opposed to the expansion of the lung may be considered under the label "atelectasis." The half-chest cage in which the resorption is to occur is made up of the rib cage, the diaphragm and the mediastinum. The mediastinum and diaphragm can be pulled into the half chest to a considerable degree. Also, approximation and bending of the ribs may contribute to the diminution of space. Again, for simplicity, this rigidity of the chest wall opposing its being pulled into the chest cavity may be regarded as the rigidity of the "mediastinum" against lateral shift.

The action of the three forces is presented diagrammatically in Figure 2. In the resorption of a large pleural effusion three different developments are possible. In the first place the resorbing pull is large, the atelectatic resistance of the lung against expansion is weak and the mediastinum and the other constituents of the half chest wall are stable and firm. This represents the ideal development. The exudate is resorbed and the lung is completely

expanded without displacement of the mediastinum and deformity of the chest. Secondly, the atelectatic condition of the lung — or fibrous or pleural rigidity — cannot be overcome. The resorbing pull, although strong, cannot expand the lung but is powerful enough to attract the mediastinum, as well as the diaphragm and ribs. This occurs in cases in which

became fibrosed, the lobar bronchi were patent and ended in few large bronchiectatic cavities (Fig 3). The mediastinum, however, yielding to the absorption pull, shifted over to the right, and the left lung, overlapping into the right half chest, occupied the space made free by the contracting right lung. Thus, the right pleural cavity gradually decreased in size and allowed the empyema to be resorbed.

CASE 2 This patient with tuberculosis of the upper lobe was treated with artificial pneumothorax. Pleural exudate



FIGURE 4 Case 2

This roentgenogram shows spontaneous hydropneumothorax after perforation into a bronchus of a chronic pleural empyema. The arrow indicates the fluid level.

the pleural effusion is finally resorbed, the mediastinum is displaced, the chest is grossly deformed and the lung remains in atelectatic fibrosis with or without secondary changes, such as bronchiectasis. The third possible development occurs when the resorbing pull is too weak to overcome the atelectatic rigidity of the lung and also too weak to move the mediastinum, the diaphragm and the ribs. The pleural cavity is not reduced in size, and the empyema is not resorbed. This situation is quite similar to that in any abscess in a rigid cavity.

The following cases represent, respectively, the second and third developments and a combination of all three.

CASE 1 Eighteen years before he came under observation this patient had had a pneumonia and pleural empyema, which had been treated conservatively, without open drainage. His condition did not change during the following 6 years. There was maximal retraction of the right half chest. The right lung, collapsed by the large empyema at the time of the acute disease, remained in its atelectatic condition and

developed, filling the pleural cavity, and the refilling of the pneumothorax was discontinued after 1½ years. The patient recovered completely and was re-examined repeatedly, the findings always remaining unchanged. Seven years later she suffered a serious fall, following which she started coughing up large amounts of purulent fluid. X-ray examination showed a collapsed, condensed lung and a hydropneumothorax in the rigid pleural cavity (Fig 4). This was a typical history of internal perforation of a chronic pleural exudate. The lung, collapsed during the early period of the pneumothorax treatment, underwent fibrosis and became inexpandible. Although the disease healed, the exudate could not be reduced in size owing to the rigidity of the collapsed lung and the fixation of the mediastinum.

CASE 3 This patient had a lobar pneumonia followed by empyema in 1927, incompletely treated by surgery. For many years after clinical recovery the chest condition did not change. Re-evaluation 16 years later revealed a pleural cavity of medium size, filled at the left base with thick sterile pus, and a left lower lobe that was collapsed and fibrosed, as clearly shown by the approximation and shortening of the moderately dilated bronchi (Fig 5). The complete resorption of the empyema had been mechanically prevented by the atelectatic fibrosis of the lower lobe.

The sequelae of incomplete or absent expansion of the lung have occasionally been effectively prevented or combated by the institution of breathing exercises (Hofbauer⁷). If the pain and the reflex inhibition are overcome, if the weakened respiratory muscles

With the present-day penicillin treatment both these difficulties are eliminated. The disease manifested by systemic signs and symptoms has a much shorter course and is usually overcome within one or two weeks. The temperature and pulse rate



FIGURE 5 Case 3

This film shows a residual pleural empyema, sixteen years after incomplete surgical treatment. The bronchogram reveals the collapsed atelectatic lower lobe and the lingula of the upper lobe.

of the involved half chest are put to active work and if the atelectatic lung is forcefully reventilated, it recovers its elasticity, expands and resumes its full function, facilitating mechanically the resorption of the residual pleural exudate. Such a regime has met with two adverse factors. The duration of the disease was long under incomplete surgical and conservative medical treatment, and there was ample time for the development of irreparable alterations in the lung and pleura, furthermore, the systemic signs and symptoms of active disease subsided slowly and almost imperceptibly, making it difficult to determine the time when active exercises could safely be begun.

return to normal levels, the appetite returns and the patient feels well. There may still be dyspnea, owing to the restricted breathing surface. There has not been much time for the establishment of irreparable damage to the lung and pleura. In addition, because of the rapid and more dramatic improvement, the time to start with active breathing exercises can be more easily chosen. Whether the patient will be restored to active physical work or fitted again for full respiratory capacity by breathing exercises may be determined according to the individual case. Such exercises are well known to the physiotherapists, they have been used successfully in European countries in the past and more recently

they have been given greater attention in the United States. Harken,⁸ in a recent review of the activities of the Thoracic Center of a United States Army hospital group in England, placed strong emphasis on the remedial breathing exercises for chest injuries

* * *

Under the influence of penicillin it appears that the future treatment of pleural empyema will be, for a large number of cases, nonsurgical. Whether or not the systemic administration of penicillin is reinforced by local injection of the drug into the empyema cavity, the most complete evacuation of the empyema by repeated pleural taps should be attempted. After the successful treatment of the disease, care of a residual sterile empyema should not be left to the body. Empyema should not be considered cured until there is complete re-expansion of the lung. Resorption is often delayed or impeded by atelectasis of the lung or — to a lesser degree — fibrous deposits on the pleura. Re-expansion and

restoration of the ventilatory capacity of the lung mechanically facilitate the resorption of exudate and prevent or reduce permanent invalidity of the lung and chest deformities. This reactivation of the lung can be promoted by proper breathing exercises

REFERENCES

- 1 Fleischner, F. Atelectase und Pleuritis. *Wien klin Wchnschr* 49: 1092-1096, 1936
- 2 Idem. Über verschiedenes Verhalten der viszeralen und der parietalen Pleura bei Pleuritis und Pneumothorax. *Wien klin Wchnschr* 46: 1486-1488, 1933
- 3 Samson, P. C., Burford, T. H., Brewer, L. A. III and Burbank, B. Management of war wounds of chest in base center: role of early pulmonary decortication. *J Thoracic Surg* 15: 130, 1946
- 4 Altschule, M. D. and Zamcheck, N. Effects of pleural effusion on respiration and circulation in man. *J Clin Investigation* 23: 325-331, 1944
- 5 Lundblom, A. F. Über die Funktionsfähigkeit der mit Pneumothorax artificialis behandelten Lunge nach ihrer Wiederentfaltung. *Acta med Scandinav* Supp 15: 143, 1926
- 6 Rösle, R. Die pathologisch anatomischen Grundlagen der Epituberkulose. *Virchows Arch f Path Anat* 296: 138, 1935
- 7 Hofbauer, L. *Atmungspathologie und Therapie*. 336 pp. Berlin: Julius Springer, 1921
- 8 Harken, D. E. Review of activities of thoracic center for III and IV hospital groups, 160th General Hospital, European Theater of Operations. *J Thoracic Surg* 15: 31-43, 1946

MEDICAL PROGRESS

ELECTROCARDIOGRAPHY*

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IN 1940 a progress report was published to help orient physicians in general regarding the value and limitations of electrocardiography in the diagnosis and evaluation of heart disease.¹ The present article is not strictly a progress report. Rather, it is designed for those who have some basic knowledge of the subject but who have lacked time and opportunity to keep abreast of the recent developments in the field. No attempt has been made to review completely the voluminous number of articles that have been published in recent years, only a few major points are considered.

A recent development has been the perfecting of an electrocardiographic apparatus that inscribes the final record directly on paper instead of through the medium of photography. The practical advantages are obvious in providing a tracing that is immediately available at the bedside and obviates the trouble and expense of photographic developing. It remains to be seen whether technical difficulties and objections have been sufficiently overcome so that these machines will be reliable and sturdy enough for clinical use. All of them employ the audion-tube method of amplification, and most of them

inscribe the record by a heated stylus that melts a wax or plastic surface on the paper. At least one, however, utilizes an ink-writing device. There are at least four different models of these new machines currently on the market.

In the past few years emphasis in electrocardiographic studies has to some extent shifted. The period from the early 1920's until late in the 1930's was the halcyon time for descriptive, empirical electrocardiography. Many valuable data were amassed concerning electrocardiographic variations in different types of heart disease, and this technique in the assessment of various arrhythmias was particularly explored in voluminous detail. Moreover, during this period, the value of the electrocardiogram in the diagnosis of myocardial infarction was increasingly established.

In recent years more and more scrutiny has been given to the basic electrical principles involved and to correlations between clinical findings and experimental work. In a way this is a harking back to much of the fundamental work that was done in the field, especially by Sir Thomas Lewis. The painstaking work of Wilson and his collaborators*,^{2,3} through the years on the laws governing the electrical effects produced by the heart beat and especially on precordial and direct leads has now received the general recognition it merits. Today, no cardiac

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specialist would be considered really competent who was not conversant with some of the electrical principles underlying clinical electrocardiography. Bayler⁴ has presented a review of some of these basic electrical correlations, including vector analysis.

ELECTROCARDIOGRAPHIC VARIATIONS IN THE ABSENCE OF ORGANIC HEART DISEASE

It has been recognized for a long time that serious heart disease can exist with a normal electrocardiogram. In a recent study of 722 patients with heart disease, 223 had normal electrocardiograms.⁵ The converse situation has been less appreciated, but numerous recent articles testify to the relative frequency of abnormal tracings in persons with no detectable heart disease, as well as of the various extracardiac conditions that can alter the record. Thus, in observations on 500 unselected young adults, of whom only 14 had any clinical evidence of heart disease, Viscidi and Geiger⁶ found that 48.8 per cent had normal electrocardiograms. Most of the abnormalities were, it is true, minor. In a study of 1000 healthy aviators, Gravbiel et al.⁷ reported that the PR interval was less than 0.12 second in 13 cases and longer than 0.20 second in 16. The QRS interval exceeded 0.10 second in 35 cases, including 1 case of frank left bundle-branch block and 2 of the Wolff-Parkinson-White pattern. Other deviations from the normal were also reported. Stewart and Manning⁸ noted essentially similar results. In an analysis of electrocardiograms of 500 Canadian flyers 18 per cent were found to be borderline or abnormal and thus confirmed a previous study.⁹ Abnormal PR intervals were observed in 5 per cent, abnormal Q waves in 2 to 3 per cent, and diphasic or negative T₁ or T₂ waves in 0.5 to 1 per cent.

Elevation of the diaphragm and change of posture may alter the form and produce inversion of the T waves in the standard leads as well as the precordial leads.^{10, 11} This occurs especially in the upright position. It is seen particularly in persons with neurocirculatory asthenia.¹²⁻¹⁶ One explanation is that the inversion is due to a change in the position of the heart, but Wendkos^{15, 16} is of the opinion that it is the result of heightened sympathetic activity in the upright position. Some support for his thesis is found in the fact that the assumption of the upright position may shorten the PR interval.^{17, 18} Intra-abdominal disease can alter the form of the electrocardiogram,¹⁹ and even the eating of a meal may produce minor changes in the P and T waves,²⁰ which in borderline records might easily be interpreted as being due to acute heart disease. The difficulty of distinguishing between acute upper abdominal disease and acute cardiac accidents is well known, as is the frequency with which they may coexist.

What then are the bounds of normal in electrocardiography, since records that fall outside con-

ventional standards may be obtained from apparently normal persons? There is no final answer. These standards must still be accepted as being the best available. It is well to appreciate, however, that the electrocardiogram should be interpreted with caution, it is a useful adjunct in clinical diagnosis, but its findings should always be related to the clinical picture. As many mistakes are made from an overenthusiastic and undercritical reliance on electrocardiography as from a failure to utilize this technical aid.

It has been known for a long time that electrocardiographic changes occur in the course of rheumatic fever, and hence the electrocardiogram has been relied on a good deal in the differential diagnosis of this disturbance. Is it reasonable to assume therefore, that when electrocardiographic abnormalities occur in patients following acute respiratory infections, rheumatic fever is present? Rantz, Boisvert and Spink²¹ found that such changes occurred in 10.8 per cent of 185 patients with acute hemolytic streptococcus throat infections. These changes consisted of prolongation of the PR interval or of sharp inversion of the T waves, often in all three leads. These authors believed that rheumatic fever only follows hemolytic streptococcus infection and that the many manifestations that may occur, such as arthritis, fever and carditis, should be grouped together under the term "poststreptococcal state." It is the opinion of many authors that such electrocardiographic changes following infections are often nonspecific.^{22, 23} They have been found during and after pneumococcal pneumonia — a disease that is seldom associated with rheumatic fever.²⁴ Sometimes, following such infections of varied etiology, clinical myocarditis or pericarditis develops, and this may even be fatal.²⁵⁻²⁸ The administration of the sulfonamides has on occasion been accused of producing myocarditis or diffuse vascular disease.²⁹⁻³³ In such cases electrocardiographic changes may be the clue to the developing disease. Therefore, it can be seen that, useful as this technic is in the diagnosis of rheumatic fever, caution is necessary because of the possibility that nonspecific changes in the tracings may occur.

Many drugs may alter the form of the electrocardiogram. For a detailed enumeration of the abnormalities that may follow drug administration the reader is referred to the table in the text of Graybiel and White.³⁴

MULTIPLE PRECORDIAL LEADS

Electrocardiography has to some extent developed the hard way. The three standard leads were introduced first, and for years electrocardiographic interpretation was based on analyses of these leads alone. The standard leads, however, are complex in that they represent the difference between the electrical potentials at two points of the body remote from the heart — for example, Lead I is the difference be-

tween the left arm and the right arm. Hence, the interpretation of such records is not simple, although it is made easier by the assumptions implicit in the Einthoven triangle hypothesis. Unipolar leads that register the potential at one point and in which the second or indifferent electrode is at zero potential offer many advantages. Precordial and other chest leads, although not strictly unipolar, at least approach that situation. By the taking of such records at numerous points on the surface of the chest (and also on occasion from the esophagus), more exact information may be elicited regarding the presence and localization of cardiac lesions than can be obtained from the standard leads. A committee of the American Heart Association³⁵ has recognized the value of such multiple precordial leads by recommending that they be taken, as suggested by Wilson, at six points across the chest. If it is not feasible to take the six leads, the committee recommends that at least three — for example, C_1 , C_2 and C_3 — be obtained, some workers prefer C_1 , C_4 and C_5 . There is no agreement about which indifferent electrode is the best — that in the right arm, the left leg, the Wilson central terminal, the right scapular and so forth. Most authorities, however, accept the central terminal electrode of Wilson³⁶ as the one that most nearly approaches zero potential throughout the cardiac cycle.^{2, 3, 36-39} Wolferth,⁴⁰ who does not accept the validity of the Einthoven triangle hypothesis, disagrees.

In general, what type of information do multiple precordial leads furnish that cannot be gained as satisfactorily from the standard leads in addition to a single apical lead with which doctors are much more familiar? Their chief value is, of course, in the diagnosis of the presence and extent of anterior myocardial infarction. The earliest evidence of this condition may appear in the leads over the right side of the precordium and may continue to be limited to this area.^{2, 41} The findings in these leads may permit a definite diagnosis that might be missed altogether or could only be suspected from the standard leads or a single apical lead.

Multiple precordial leads are also useful in diagnosing bundle-branch block, particularly incomplete or atypical patterns.^{2, 3} In such leads there is a delay in the activation of the ventricle on the side of the block that will be registered by broad, notched or bifid R waves in the precordial leads over the ventricle on the blocked side.

Some assistance in the diagnosis of ventricular hypertrophy can also be obtained from multiple precordial leads.² The patterns seen in the standard leads may be confused with those in bundle-branch block or in normal hearts showing axis deviation, or the picture may be complicated by a combination of abnormalities. In normal hearts, even with axis deviation, the precordial leads are normal. With hypertrophy, on the other hand, the R wave is frequently unusually high in the leads taken over the

enlarged ventricle, with a small S wave, whereas the inverse pattern is found over the opposite side.

When a combination of abnormalities is present, such as myocardial infarction in addition to bundle-branch block or ventricular hypertrophy, and in other situations in which the standard leads are confusing, multiple precordial leads often enable a definite diagnosis to be made.^{2, 3}

UNIPOLAR EXTREMITY LEADS

Since the introduction of unipolar extremity leads⁴² and the extensive studies of Goldberger⁴³⁻⁴⁵ on this subject, there has been a gradually increasing appreciation of their clinical value. Such leads are of considerable assistance in judging the position of the heart in the thoracic cavity.² It has been shown that extremity leads register predominantly electrical potentials from the surface of the heart nearest them. Thus, the right-arm lead is usually negative, since facing it are the great valvular orifices, which tend to convey the potential of the ventricular cavities. The patterns of the left-leg and left-arm leads will resemble those found in precordial leads over the right or left ventricle, depending on whether the heart lies transversely or vertically. Occasionally, confusing patterns are present in the standard limb and precordial leads, as in anterior myocardial infarction with changes in Lead 3. In such cases the position of the heart may be responsible, and help may be obtained from unipolar extremity leads.

Extremity leads may also be of value in the diagnosis of posterior myocardial infarction when the standard leads are equivocal and the precordial leads are normal, and in other conditions in which a prominent Q_2 is present that may or may not represent heart disease, as mentioned below. Goldberger⁴⁴ has discussed their usefulness at considerable length.

DEEP Q_2 PATTERN

It is often of considerable practical importance to know whether variants seen in the standard leads are due to shifts in the electrical axis of the heart or to pathologic changes. This is especially true with the so-called "deep Q_2 " pattern, which may be a normal variant seen in transversely lying hearts or the only sign of recent or old posterior myocardial infarction. Esophageal leads most readily give the answer,⁴⁷ but such leads are often impracticable.

Pardee,⁴⁸ who originally pointed out the significance of the deep Q_2 pattern, stated that for such a wave to have a pathological import, it must have an amplitude at least 25 per cent as great as that of the largest QRS complex, and he also noted that in normal persons it tended to diminish with descent of the diaphragm. Lyle⁴⁹ observed that the disappearance of Q_2 on inspiration is proof that it is positional, although the converse does not hold. Ungerleider⁵⁰ did not agree with Lyle. Lyle also found that unipolar extremity leads were helpful in evaluating the size of the true Q wave. Myers and

Oren⁵¹ employed the left-leg lead in helping to distinguish between abnormal and normal Q_2 patterns, and found that when Q_{LL} had 25 per cent or more of the amplitude of R_{LL} a diagnosis of posterior infarction could be suspected. Goldberger,⁵² in an extensive article on the differentiation of normal from abnormal Q waves, came to the conclusion that posterior infarction was usually present if the Q_{LL} was 40 per cent or more of the entire QRS complex or 60 per cent of R_{LL} and was 0.04 second or more in duration, in association with a downward T wave and provided the QRS_{LL} pattern was not of the QS or W type. Ungerleider,⁵⁰ in a recent review of 1355 cases found that one or more of the following abnormalities were present in 94 per cent of cases with a deep Q_2 due to coronary disease, as compared to only 24 per cent of normal subjects: weight less than 5 per cent overweight, absence of S_1 , Q_2 more than 1 mm in depth, T_2 less than 1 mm tall, Q_2 of 0.04 second or more in duration, Q_2 of 75 per cent or more of the tallest R wave in the limb leads, and deep inversion of T_2 , exceeding 25 mm. Ungerleider was of the opinion that there is no need to employ unipolar leads in routine electrocardiography. Nyboer⁵³ took exception to these criteria, since he found them present in a substantial percentage of normal persons, especially those with horizontally lying hearts. He suggested that two or more of these impairments be required in the evaluation of the Q_2 and furthermore that chest and other exploratory leads may be required.

MAIN DEFLECTION DOWNWARD IN ALL STANDARD LEADS

Goldberger⁵⁴ has discussed the possible causes of electrocardiograms in which the main ventricular deflections are downward in the three standard leads. These are as follows: marked right-axis deviation, anterior infarction combined with marked left-axis deviation, posterior infarction combined with marked right-axis deviation, and combined anterior and posterior infarction. The last three of these show characteristic Q waves, which, in distinction to the S waves of axis deviation, help to distinguish them. Assistance may also be obtained from unipolar extremity leads.

ATYPICAL MYOCARDIAL INFARCTION AND THE ENDOCARDIAL ELECTROCARDIOGRAM

In 1938 Wood, Wolferth and Bellet⁵⁵ described an electrocardiographic pattern present in infarction of the lateral wall of the left ventricle, consisting of depression of the RST segments in Lead 4 and usually in Leads 1 and 2. Thomson and Feil⁵⁶ found 19 cases of lateral infarction in 136 cases examined at autopsy. Nine were recent, and in 4 the pattern described above was present. In this connection attention should be called to an experimental study by Wolferth et al.⁵⁷ on positive and negative displacements of the RST segments in which positive displacements are classified as primary because they

occur as the result of abnormal current flow originating in close relation with the exploring electrode, whereas negative displacements are secondary because they result from the abnormality originating in other parts of the ventricle. The negative RST segments may occur when there is involvement extending to the epicardial surface at a point away from the exploring electrode, as in lateral infarction, or when the lesion is confined to the endocardial aspects of the ventricular wall, even when this underlies the exploring electrode. Bayley⁵⁸ has cited a case in which injury was confined to the endocardial surface of the left ventricle that showed RST depression, and he, like the others, mentioned that such findings are seen in myocarditis, atypical myocardial infarction and angina pectoris. In two recent reports electrocardiograms were obtained on human beings with the exploring electrode introduced into the auricular and ventricular cavities by means of cardiac catheterization.^{59, 60} The findings confirmed experimental work on animals regarding the nature of the endocardial electrocardiogram.

Pardee and Goldenberg⁶¹ found that infarctions of the anterior wall of the left ventricle without subepicardial necrosis had atypical patterns that might resemble those described above in lateral infarctions. The typical changes in the ST segment and T wave occurred most frequently when the septum was involved, with or without necrosis of the wall of the ventricle itself.

When negative displacement of the ST segment occurs and myocardial infarction is suspected clinically, the injury may be either limited to the endocardial surface or remote from the exploring electrodes, as in lateral infarction. Help in differentiating the two may be gained at times by means of the use of precordial leads high in the chest, which may show positive displacements of the ST segment and typical changes in the QRS complex.⁶²

VENTRICULAR HYPERTROPHY

Another problem that vexes electrocardiographers is the determination of early degrees of ventricular hypertrophy. It is admitted that the electrocardiogram frequently gives evidence of left ventricular hypertrophy in patients with hypertension or other conditions producing left ventricular strain earlier than x-ray or other clinical measurements, but borderline cases are difficult to evaluate, since left-axis deviation is often present with normal hearts and left ventricular hypertrophy may exist with a normal axis. Indeed, in its early stages, the left axis that is usually present is probably due to the fact that the majority of such hearts lie transversely.

Mention was made above of the help to be gained from multiple precordial leads. Various investigators have laid down criteria for the diagnosis of left ventricular hypertrophy. Thus, Gubner and

Ungerleider⁶³ stated that left ventricular enlargement can be considered to be present when left-axis deviation occurs with any of the following when R_1 plus S_1 equals 25 mm or more, when there is any depression of ST_1 , even as slight as 0.5 mm, and when T_1 is less than 1.0 mm in height. And they further state that left-axis deviation is not a necessarily integral part of the pattern of left ventricular hypertrophy. White and his associates⁶⁴⁻⁶⁶ have traced the development of the electrocardiographic pattern in patients with hypertension and compared its frequent regression after lumbodorsal sympathectomy with the lack of improvement in patients treated in other ways. They reported findings in the limb leads similar to those mentioned above. In addition, they noted that half their cases showed abnormal T waves in Leads CF_4 and CF_5 , and in 24 per cent high voltage of the precordial QRS complexes existed.

ARRHYTHMIAS

Decherd, Ruskin and Brindley⁶⁷ cited a case showing interatrial block — a rare finding. A similar case has recently been seen at the Boston City Hospital.⁶⁸

Parsonnet et al⁶⁹ have published an elaborate classification of bigeminal rhythm in which twenty-nine mechanisms that may produce this phenomenon are described.

That cardiac arrhythmias may follow operations on the chest is becoming increasingly appreciated.⁷⁰⁻⁷² They may develop in connection with operation on the pleura, the lung or the heart. These arrhythmias may take the form of auricular fibrillation, flutter, frequent premature auricular beats, wandering pacemaker or nodal rhythm. They may occur during the operation or may be delayed for some days, and may be associated with the development of pulmonary infarction.

Evans⁷³ has advanced the theory that paroxysmal auricular tachycardia and flutter are the same, and that cases usually diagnosed as paroxysmal tachycardia have a 2:1 auriculoventricular block. Decherd, Ruskin and Herrmann⁷⁴ have, however, concluded from a study of momentary atrial electrical axes that in supraventricular tachycardia there is a single ectopic focus rather than a circus movement, as in auricular flutter and fibrillation.

SUMMARY

A résumé of certain recent developments in the field of electrocardiography is presented. In particular, electrocardiographic abnormalities in persons without organic heart disease, multiple precordial and unipolar extremity leads, atypical myocardial infarction, the deep Q_1 pattern and ventricular hypertrophy are discussed.

REFERENCES

1. Ellis, L. B. Electrocardiography in general medicine. *New Eng J Med* 222:1078-1085, 1940.
2. Wilson, F. N., Johnston, F. O., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Corrin, N., deOliveria, R. M., Scaris, R., and Barker, P. S. Precordial electrocardiogram. *Am Heart J* 27:19-85, 1944.
3. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., and Barker, P. S. On Einthoven's triangle, theory of unipolar electrocardiographic leads, and interpretation of precordial electrocardiogram. *Am Heart J* 32:277-310, 1946.
4. Bayley, R. H. On certain applications of modern electrocardiographic theory to interpretation of electrocardiograms which indicate myocardial disease. *Am Heart J* 26:769-831, 1943.
5. Pazzanese, D., and Bertacchi, S. Normal electrocardiograms in cardiovascular disease. *Am Heart J* 31:33-52, 1946.
6. Visconti, P. C., and Geiger, A. J. Electrocardiographic observations on 500 unselected young adults at work. *Am Heart J* 26:763-768, 1943.
7. Graybiel, A., McFarland, R. H., Gates, D. C., and Webster, F. A. Analysis of electrocardiograms obtained from 1000 young healthy aviators. *Am Heart J* 27:524-549, 1944.
8. Stewart, C. B., and Manning, G. W. A detailed analysis of electrocardiograms of 500 R.C.A.F. aircrew. *Am Heart J* 27:501-523, 1944.
9. Hall, G. E., Stewart, C. B., and Manning, G. W. Electrocardiographic records of 2000 R.C.A.F. aircrew. *Canad M A J* 46:226-230, 1942.
10. White, P. D., Chamberlain, F. L., and Graybiel, A. Inversion of T waves in lead II caused by variation in position of heart. *Br. Heart J* 3:233-240, 1941.
11. Scherf, D., and Weissberg, J. Alterations of T-waves caused by change of posture. *Am J M Sc* 201:693-703, 1941.
12. Graybiel, A., and White, P. D. Inversion of T wave in lead I or II of electrocardiogram in young individuals with neurocirculatory asthenia with thyrotoxicosis, in relation to certain infections, and following paroxysmal ventricular tachycardia. *Am Heart J* 19:345-354, 1935.
13. Master, A. M. Effort syndrome or neurocirculatory asthenia in Navy. *U S Nav M Bull* 41:666-669, 1943.
14. Logue, R. B., Hanson, J. F., and Knight, W. A. Electrocardiographic studies in neurocirculatory asthenia. *Am Heart J* 28:574-577, 1944.
15. Wendkos, M. H. Influence of autonomic imbalance on human electrocardiogram. I. Unstable T waves in precordial leads from emotionally unstable persons without organic heart disease. *Am Heart J* 28:549-567, 1944.
16. Wendkos, M. H., and Logue, R. B. Unstable T waves in leads II and III in persons with neurocirculatory asthenia. *Am Heart J* 31:711-723, 1946.
17. Manning, G. W., and Stewart, C. B. Alteration in P-R interval associated with change in posture. *Am Heart J* 30:109-117, 1945.
18. Holmes, J. H., and Weill, D. R., Jr. Incomplete heart block produced by changes in posture. *Am Heart J* 30:291-298, 1945.
19. Clarke, N. E. Electrocardiographic changes in active duodenal and gall bladder disease. *Am Heart J* 29:628-632, 1945.
20. Simonson, E., Alexander, H., Henschel, A., and Kety, A. Effect of meals on electrocardiogram in normal subjects. *Am Heart J* 32:202-214, 1946.
21. Rantz, L. A., Bolvert, P. J., and Spink, W. W. Etiology and pathogenesis of rheumatic fever. *Arch. Int. Med* 76:131-138, 1945.
22. Campbell, M. Latent heart block. *Brit. Heart J* 5:163-181, 1943.
23. Young, D. Electrocardiographic changes occurring during upper respiratory infections. *Am Heart J* 32:383-393, 1946.
24. Thomson, K. J., Rustein, D. D., Tolmach, D. M., and Walker, W. H. Electrocardiographic studies during and after pneumococcus pneumonia. *Am Heart J* 31:565-579, 1946.
25. Saphir, O. Myocarditis: general review, with analysis of 240 cases. *Arch. Path* 32:1000-1051, 1941 and 33:88-137, 1942.
26. Finland, M., Parker, F. Jr., Barnes, M. W., and Jolliffe, L. S. Acute myocarditis in influenza A infections: two cases of nonbacterial myocarditis, with isolation of virus from lungs. *Am J M Sc* 209:455-468, 1945.
27. Candel, S., and Wheelock, M. C. Acute non specific myocarditis. *Ann. Int. Med* 23:309-337, 1945.
28. Nathan, D. A., and Dathie, R. A. Pericarditis with effusion following infections of upper respiratory tract. *Am Heart J* 31:115-130, 1946.
29. French, A. J., and Weller, C. V. Interstitial myocarditis following clinical and experimental use of sulfonamide drug. *Am J Path.* 18:109-121, 1942.
30. Lederer, M., and Rosenblatt, P. Death during sulfathiazole therapy. Pathologic and clinical observations on four cases with autopsies. *J A M A* 119:8-18, 1942.
31. Rich, A. R. Role of hypersensitivity in periarthritis nodosa as indicated by seven cases developing during serum sickness and sulfonamide therapy. *Bull. Johns Hopkins Hosp* 71:123-140, 1942.
32. *Idem*. Additional evidence of role of hypersensitivity in etiology of periarthritis nodosa: another case associated with sulfonamide reaction. *Bull. Johns Hopkins Hosp* 71:375-379, 1942.
33. Wells, A. H., and Sax, S. G. Isolated myocarditis: probably of sulfonamide origin. *Am Heart J* 30:522-526, 1945.
34. Graybiel, A., White, P. D., Wheeler, L., and Williams, C. *Electrocardiography in Practice*. Second edition. 458 pp. Philadelphia: W. B. Saunders Co., 1946. P. 235.
35. Committee of American Heart Association. Standardization of precordial leads: supplementary report. *Am Heart J* 15:235-239, 1938. *Idem*. Second supplementary report by Committee of American Heart Association for standardization of precordial leads. *Ibid* 25:535-538, 1943.
36. Wilson, F. N., MacLoud, A. G., Johnston, F. D., and Barker, P. S. Electrocardiograms that represent potential variations of single electrode. *Am Heart J* 9:447-471, 1934.
37. Goldberger, E. Validity of Einthoven triangle hypothesis. *Am. Heart J* 29:369-377, 1945.

18. Ashman R, Ferguson F P, Gremillion A J and Byer E. Normal human ventricular gradient V. Relationship between AQRS and G and potential variations of body surface *Am Heart J* 29: 697-703 1945
39. Carral, R. Estudio critico de algunos argumentos vertidos en contra de la fidelidad de las derivaciones unipolares *Arch Inst cardiol Mexico* 15 161-178 1945
40. Wolferth C. C. and Lavezey M. D. Study of methods of making so-called unipolar electrocardiograms *Am Heart J* 27 764-782, 1944
41. Rosenbaum F F, Wilson F N., and Johnston F D. Changes in precordial electrocardiogram produced by extension of antero-septal myocardial infarction *Am Heart J* 30 11-18 1945
42. Kossmann, C. E. and Johnston F D. Precordial electrocardiogram I. Potential variations of precordium and of extremities in normal subjects *Am Heart J* 10 925-941 1935
43. Goldberger E. Simple indifferent electrocardiographic electrode of zero potential and technique of obtaining augmented unipolar, extremity leads *Am Heart J* 23 483-492, 1942
44. *Idem.* aVr and aVf leads: simplification of standard lead electrocardiography *Am Heart J* 24 378-396, 1942.
45. *Idem.* Use and advantages of augmented unipolar extremity leads (aV-leads) in electrocardiographic diagnosis of myocardial infarction (due to coronary artery occlusion and acute coronary insufficiency) *New York State J Med* 43:961-986 1943
46. *Idem.* Studies on unipolar leads. IV. Effects of digitalis *Am Heart J* 28 370-377 1944
47. Nyboer J. Normal and abnormal esophageal electrocardiogram with particular reference to myocardial infarction *Am Heart J* 22 469-493 1941
48. Pardee H. E. B. Significance of electrocardiograms with large Q in lead 3 *Arch Int Med* 46 470-481 1950
49. Lyle A. M. Further observations on deep Qs of electrocardiogram *Am Heart J* 28 199-216 1944
50. Ungerleider H. E. Electrocardiogram in practical risk appraisal *Proc 34th Annual Meet Medical Section of American Life Convention* 1946 Pp 73-86
51. Myers G B., and Oren B. G. Use of augmented unipolar left leg lead in differentiation of normal from abnormal Q wave in standard lead III *Am Heart J* 29 708-727, 1945
52. Goldberger E. Differentiation of normal from abnormal Q waves *Am Heart J* 30 341-365 1945
53. Nyboer J. Discussion of Ungerleider 50 Pp 87-98
54. Goldberger E., and Schwartz, S. P. Electrocardiograms in which main ventricular deflections are directed downward in standard leads *Am Heart J* 29 62-70 1945
55. Wood, F. C., Wolferth C. C., and Bellet S. Infarction of lateral wall of left ventricle: electrocardiographic characteristics *Am Heart J* 16 387-410 1938
56. Thomson H W. and Feil, H. Infarction of lateral wall of left ventricle: pathologic and electrocardiographic study *Am J M Sc* 207:588-600 1944
57. Wolferth C. C. Bellet S., Lavezey M. M., and Murphy F. D. Negative displacement of RS-T segment in electrocardiogram and its relationships to positive displacement: experimental study *Am Heart J* 29 220-245 1945
58. Bayley, R. H. I. Electrocardiographic effects of injury at endocardial surface of left ventricle *Am Heart J* 31 677-684 1946
59. Lenegre J., and Maurice P. Some results of recording electrical currents from right auricle and ventricle by the direct intracavity lead *Am Heart J* 32 401 1946 (*Abstr*)
60. Hecht H. H. Potential variations of right auricular and ventricular cavities in man *Am Heart J* 32 39-51 1946
61. Pardee H. E. B. and Goldenberg M. Electrocardiographic features of myocardial infarction as affected by involvement of septum and by complete and incomplete transmural involvement. *Am Heart J* 30 367-381 1945
62. Rosenbaum F F, Wilson F N. and Johnston F D. Precordial electrocardiogram in high lateral myocardial infarction *Am Heart J* 32 155 151 1946
63. Gubner R. S. and Ungerleider H. E. Electrocardiographic criteria of left ventricular hypertrophy: factors determining evolution of electrocardiographic patterns in hypertrophy and bundle branch block *Arch Int Med* 72 196-209 1945
64. Evans E. Mathews M. W. and White P. D. Electrocardiogram in hypertension I. Its description *Am Heart J* 30 140-165, 1945
65. White P. D. Smithwick R. H., Mathews M. and Evans E. Electrocardiogram in hypertension II. Effect of radical lumbodorsal sympathectomy (preliminary report) *Am Heart J* 30 165 188, 1945
66. Canabal E. J. Thomson H. F. W. and White F. D. Electrocardiogram in hypertension III. Electrocardiograms of hypertensive patients followed for long time without splanchnic resection in comparison with those in patients who had had splanchnic resection *Am Heart J* 30 189-194, 1945
67. Decherd G. M., Jr., Ruskin A., and Brindley P. Interatrial and sinoatrial block, with illustrative case. *Am Heart J* 31 352-363 1946
68. Bloomfield R. A. Unpublished data
69. Parsonnet A. E., Miller R., Bernstein A., and Kloss E. Bigeminy: electrocardiographic study of bigeminal rhythms. *Am Heart J* 31 74-92 1946
70. Bailey C. C. and Betts R. H. Cardiac arrhythmias following pneumonectomy *New Eng J Med* 229 356-359 1943
71. Currens J. H., White, P. D., and Churchill E. D. Cardiac arrhythmias following thoracic surgery *New Eng J Med* 229:360-364 1943
72. Harken D. E. and Zoll P. M. Foreign bodies in and in relation to thoracic blood vessels and heart. III. Indications for removal of intracardiac foreign bodies and behavior of heart during manipulation *Am Heart J* 32 1-19, 1946
73. Evans W. Unity of paroxysmal tachycardia and auricular flutter *Brit Heart J* 6:221-237, 1944
74. Decherd G. M., Ruskin A., and Herrmann, G. R. Momentary atrial electrical axes II. Atrial flutter atrial fibrillation and paroxysmal tachycardia *Am Heart J* 29 20-36 1945

MASSACHUSETTS MEDICAL SOCIETY

PROCEEDINGS OF THE COUNCIL

Stated Meeting, February 5, 1947

A STATED meeting of the Council of the Massachusetts Medical Society was called to order by the president, Dr Dwight O'Hara, on February 5, 1947, at 10 30 a m in John Ware Hall, 8 Fenway, Boston, Massachusetts. Two hundred and one councilors were present (Appendix No 1)

The President announced that the secretary, Dr Michael A Tighe, was absent because of illness. He expressed a wish for his speedy recovery. The President announced that for the purpose of the meeting he appointed Dr Robert N Nye as acting secretary. This appointment was confirmed by the vote of the Council. The Acting Secretary presented the record of the Council meeting held on October 2, 1946, as published in the *New England Journal of Medicine*, issue of December 12, 1946. He moved its adoption. This motion was seconded by a councilor, and it was so ordered by vote of the Council.

COMMITTEE REPORTS

Executive Committee

This report (Appendix No 2) was presented by the Acting Secretary, who moved its acceptance. This motion was seconded, and it was so ordered by vote of the Council.

Committee on Arrangements

This report, which was submitted by the chairman, Dr Sidney C Wiggan, Suffolk, was as follows:

The committee has been active since the October meeting of the Council. We have held a number of meetings, one of which was held jointly with representatives from the various sections.

From that meeting, we received many suggestions as to what topics and what speakers we should have on our program next May, and we are now in the process of arranging the program, which we can promise will be an interesting one.

The 1947 meeting will run for a full three days, instead of two and a half as last year, and this extra half-day will be given over to a program which will be devoted to a discussion of the accomplishments of the Massachusetts Medical Society in meeting the costs of sickness.

Last year, the Committee on Arrangements, under Dr Roy J Heffernan, showed a profit of \$5200. We may not be able to do quite so well this year as the Hotel Statler has increased our rental by 50 per cent and also decreased the number of exhibit booths that we may sell. However, Mr Boyd advises us that he has already sold all available booths, and we are certain we can show a substantial profit in 1947.

Owing to the increased length of the meeting, we have been able to set aside one evening exclusively for the Shattuck Lecture, instead of running it in with a general session, as we have had to do in recent years.

The committee would appreciate any suggestions from members of the Council regarding the program.

Dr Walter G Phippen, Essex South, moved the adoption of the report. This motion was seconded, and it was so ordered by vote of the Council.

Committee on Publications

This report (Appendix No 3) was offered by Dr Richard M Smith, Suffolk, chairman. Dr Smith called the Council's attention to the fact that this report contained three recommendations.

The first was that an appropriation of \$5000 be set aside on which the *New England Journal of Medicine* may draw if it becomes necessary. He moved the adoption of this recommendation. This motion was seconded, and it was so ordered by vote of the Council.

The second was that a directory of the officers and fellows of the Society be published in 1947. He moved the adoption of this recommendation. The motion was seconded, and it was so ordered by vote of the Council.

The third was that the advisability of the Society's setting up a retirement plan for its full-time employees be referred to a committee of the Society, either a special committee or an existing committee, according to the desires of the President and that if the adoption of such a scheme seems desirable a specific retirement plan be presented to the Council, subject to the approval of the Committee on Finance, if the matter was not referred to said committee. Dr Smith moved the adoption of this recommendation. This motion was seconded, and it was so ordered by vote of the Council, after the President had announced that the recommendation was approved by the Executive Committee.

Dr Smith announced that Dr William Dock, Director of Medicine, Long Island College of Medicine, Brooklyn, will deliver the 1947 Shattuck Lecture.

Dr Smith moved the adoption of the report as a whole. This motion was seconded, and it was so ordered by vote of the Council.

Committee on Public Relations

This report, which was presented by Dr Milton J Quinn, Middlesex East, a member of the committee, was as follows:

The Committee on Public Relations recommends to the Council that the committee be authorized to establish a speakers' bureau.

The Committee on Public Relations is not yet ready to report on the subject of a women's auxiliary to the Massachusetts Medical Society. The progress in this direction is that the committee has requested each member of the committee to canvass his district and report at the next meeting of the Public Relations Committee the sentiment in that district.

Dr Quinn moved the acceptance of the report. This motion was seconded by a councilor, and it was so ordered by vote of the Council. Dr Quinn pointed

out that this report contained one recommendation, namely, that the Committee on Public Relations be authorized to establish a speakers' bureau. He moved the adoption of this recommendation. This motion was seconded by Dr Phippen.

Dr Reginald Fitz raised the question whether or not the establishment of a speakers' bureau under the proposed auspices might hamper the Director of Medical Information and Education. The President said that this matter was brought to the attention of the Committee on Public Relations by the Secretary, who was being constantly called on to provide speakers for lay groups. He added that the Secretary found it difficult to obtain such speakers and expressed the thought that this means of valuable public approach should be on a sounder basis than heretofore existed. He added that the Committee on Public Relations agreed that a speakers' bureau should be set up, that the participating speakers in this bureau should come from all over the state and that this was an activity which belonged particularly to the committee. He said that the possibility of conflict with the newly proposed office had not occurred. In this connection he asked the Acting Secretary to read that part of the Executive Committee's report which had to do with this matter. The acting secretary said that the Executive Committee approved of the recommendation. He read the following from the committee's report:

The Committee on Public Relations asks the privilege of organizing this movement in the Society. It would make its selection of speakers from all parts of the state. The Executive Committee also believes that by adopting this recommendation the Council would give at least some direction to the office of the Director of Medical Information and Education and that this office might as one of its duties, work with and under the direction of the Committee on Public Relations in setting up and supervising the bureau called for in this recommendation.

Dr Frank R. Ober, Suffolk, asked if it would not be a good idea to have the bureau set up under the direction of the Director of Medical Information and Education. At this point, Dr Ober moved as an amendment to the recommendation that when and if a speakers' bureau is established it be organized by the Director of Medical Information and Education when and if such a director is elected. This amendment was seconded, and it was so ordered by vote of the Council. It was moved and seconded that a speakers' bureau be established. It was so ordered by vote of the Council.

Committee on Legislation

This report, which is as follows, was presented by Dr David L. Belding, Norfolk South, chairman:

The Committee on Legislation submits only a brief report of progress, since its activities do not begin until the Massachusetts Legislature convenes.

The first meeting of the committee was held on October 16, 1946 for the purpose of organization, since two thirds of its members were newly elected. At this meeting co-chairmen and a secretary were elected, special powers

were delegated to a small executive subcommittee, Mr Charles J. Dunn was appointed legislative counsel, the budget for the coming year was drawn up, and an analysis of the Taft Bill (S 2145) by the Subcommittee on National Legislation was approved and forwarded to the Council on Medical Service of the American Medical Association. The committee was represented on October 23, 1946, at a general conference on public-health legislation sponsored by the Massachusetts Central Health Council.

Dr Belding presented a supplementary report in which he said that his committee had examined and passed on thirty-five bills that had been introduced in the Legislature. He said that the bills which were opposed by the committee fell largely in one of three categories — those that would lower the standards of medical practice, those that would interfere with the freedom of medical research and those that would unfavorably affect the high standards at present maintained by our hospitals. He added that the Chiropractors' Bill was an example of the first, the Antivivisection Bill of the second and the bills that would throw open the doors of all hospitals to every licensed practitioner of medicine irrespective of his qualifications, of the third. Dr Belding moved the adoption of the report. This motion was seconded and it was so ordered by vote of the Council.

Committee on Finance

This report (Appendix No 4) was offered by Dr Robert W. Buck, Suffolk, chairman. He pointed out that the report was purely informational. He moved its adoption. This motion was seconded, and it was so ordered by vote of the Council. Dr Buck next presented the budget for the year 1947 (Appendix No 5). He moved its adoption. This motion was seconded, and it was so ordered by vote of the Council.

Committee on Public Health

This report (Appendix No 6) was presented by Dr Roy J. Ward, Worcester, chairman. He moved its acceptance. This motion was seconded, and it was so ordered by vote of the Council.

Dr Ward said his report contained several recommendations, the first of which was that the Council authorize the President to appoint a subcommittee of three to act as liaison between the Society and the State Department of Mental Health. He moved the adoption of this recommendation. This motion was seconded. The president reported that the Executive Committee approved of the recommendation. It was adopted by vote of the Council.

Dr Ward moved that the Council adopt the recommendations contained in the report of the Subcommittee on School Health. This motion was not seconded. The President said that this portion of the report of the Committee on Public Health provoked a good deal of discussion in the Executive Committee. He asked the Acting Secretary to read that part of the report of the Executive

Committee which relates to this subject. The latter read as follows:

In reviewing this report the Executive Committee gave first consideration to that part of the report submitted by the Subcommittee on School Health. The discussion indicated that this subcommittee came into being as the result of a mandate of the Council which was motivated by a letter that Dr. Fitz received from a committee of school executives asking that the Massachusetts Medical Society set up a committee that would study ways and means of improving medical services in schools. The Executive Committee notes that the subcommittee's principal recommendation is as follows: "To establish an effective liaison between representatives of the Massachusetts Medical Society and education officials at both state and local levels." The Executive Committee is in support of this proposal.

The Executive Committee notes that the subcommittee would activate this idea by (a) having the Massachusetts Medical Society appoint an over-all committee on school medical services and (b) having each district society appoint a local committee on school medical services, it being understood that each district would apply this principle according to the needs of the individual district.

With regard to "a," the Executive Committee recommends that the word "over-all" be deleted and that the word "advisory" be substituted. The Executive Committee is impelled to this action because it believes that the latter word more clearly describes the function of such a committee and the limitations that should govern its activities.

With regard to "b," the Executive Committee, in carrying out the same idea, recommends that the word "advisory" be placed between the word "local" and the word "committee." The Executive Committee also recommends the deletion of the following language, "it being understood that each district will apply this principle according to the needs of the individual district." The Executive Committee is impelled to this action by reason of the fact that it regards these lines as redundant.

The Acting secretary moved the adoption of the first recommendation of the Subcommittee on Public Health, with "a" and "b" as amended by the Executive Committee. This motion was seconded. Dr. Elmer S. Bagnall, Essex North, was recognized. He disapproved of that recommendation of the Executive Committee which would delete as redundant the following language, "it being understood that each district will apply this principle according to the needs of the individual district." He said that he was responsible for this language and that it was purposely used so as to permit the district committees to organize their work in a manner which would suit their individual needs. He moved as an amendment to the motion that this language be permitted to stand. This was seconded. The recommendation of the Executive Committee, subject to Dr. Bagnall's amendment, was adopted by vote of the Council.

The President called the Council's attention to the fact that this report of the Subcommittee on School Health contained thirteen additional recommendations. He said that the Executive Committee recommended that these thirteen recommendations be referred to the advisory committee heretofore authorized for further study and elucidation and that this committee's attention be directed particularly to Recommendations 11 and 12 to the end that the language of these latter recommenda-

tions be changed so as to provide that the interpretation of physical findings shall continue to be the function of the physician alone and not be shared with the school nurse. It was moved and seconded that the recommendations of the Executive Committee with regard to this part of the report be adopted. It was so ordered by vote of the Council.

The President next referred to that part of the report of the Committee on Public Health which referred to public-health personnel. This part imperatively recommended that aggressive support of Dr. Getting's proposals be given and that the aid of the Committee on Legislation be obtained in expediting his program. The report outlined these proposals as follows:

- (a) To raise the salary level of the professional personnel engaged in public health on a state and local basis
- (b) To institute a sanitary code
- (c) To provide for subsidization of local health departments when, as and if they meet standards as to personnel and program content
- (d) To promote town unions of adequate size (at least 20,000 population) to support a modern public-health and school-health program at a per capita cost of \$1.50 to \$2.50 exclusive of tuberculosis and communicable-disease control and exclusive of garbage collection

The president asked that that part of the Executive Committee report dealing with this subject be read. The Acting Secretary read from the report as follows:

The Executive Committee notes that that part of the report dealing with public-health personnel, if approved by the Council, would commit the Society in a manner in which it should not be committed. It therefore recommends that the Council take no action on this matter on the grounds that the subject is beyond the scope of the Society.

Dr. Roy J. Ward was recognized. He said that he vigorously objected to the conclusion arrived at by the Executive Committee in this matter. The State Department of Public Health, he added, established many years ago largely through the influence of this society, was in danger of losing its efficiency, if not actually breaking down, through its inability to pay salaries to its personnel in keeping with those prevailing in other states or in industry. He pointed out that other states, notably New Hampshire, already had a sanitary code. He said that the recommendations of the Committee on Public Health were in accordance with a request of the American Medical Association. Finally he expressed the thought that the Executive Committee could not have been cognizant of all the facts on this subject when it arrived at its conclusions. Dr. Ward moved the adoption of the recommendations contained in that part of the report of the Committee on Public Health dealing with the subject under discussion. This motion was seconded.

Dr. Elmer S. Bagnall, in speaking in support of the motion, quoted Dr. Lewis H. Bauer, trustee of the American Medical Association, as follows:

Training of public-health officials is important, and when they are trained they should be adequately compensated. At the present time many of these officials do not receive the income of men engaged in private practice or often in other fields of medicine. The implementing of this second point is by means of legislation.

Dr Fremont-Smith, Suffolk, expressed the thought that the figures \$1 50 and \$2 50 appearing in proposal "d" should be eliminated, it being out of place for the Massachusetts Medical Society to go into such financial details. Other than this he thought the Society should support the proposals.

Dr Donald Munro, Suffolk, said that, while he favored the support of these proposals, such support implied an obligation on the Society's part to say whence the money necessary to carrying them through was coming. He expressed the thought that the Society was not in a position to meet such an obligation.

Dr Lester M. Felton, Worcester, said that the councilors of the Worcester District Medical Society, at a meeting held previous to this one, declared themselves as opposed to the implied recommendation of the Committee on Public Health. He added that it was a bad precedent to create and that if it were created, medical personnel employed by the state generally might request and reasonably expect similar backing.

Dr Reginald Fitz, Suffolk, asked if there were bills along the lines of discussion now before the General Court and if so what was the opinion of the Committee on Legislation with regard to them.

Dr Belding said that there were certain bills of this character before the Legislature. He mentioned a bill that would set up a sanitary code and said that his committee had favored it. He added that there were innumerable other bills that were largely departmental in character. The Committee on Legislation had taken no action on these bills, although it was in sympathy with the principles contained in many of them, because it believed that it was unwise to spread its activities out too thinly lest its effectiveness and strength be correspondingly weakened.

Dr Richard M. Smith said he would like to endorse what Dr Ward had said and to emphasize the fact that the Commonwealth cannot have good public-health service unless those who render the service are adequately compensated.

Dr Vlado A. Getting, Middlesex South, was recognized and spoke as follows:

I should like to state that I am appearing here not for any personal gain but in the interests of the people of the Commonwealth. In the first place, any increases in salaries that are contemplated would amount to less than 0.5 per cent of the total state budget. It is the duty of the Legislature, the Great and Honorable General Court of Massachusetts, to find ways of raising money. It is the duty of the medical profession to give leadership and to give guidance to the General Court in matters of public health, and it is not the duty of the Society or of the Department of Public Health to tell the General Court how to arrange its tax structure.

I should like to call the attention of members of the Council to the Society's bulletin *Digest, By-Laws, Code of Ethics and Medical Deference Act of the Massachusetts Medical Society*. There are many references to public health, but I shall refer to only one. On page 38, Chapter IV, Section 1, it states "Physicians, as good citizens, and because their professional training specially qualifies them to render this service, should give advice concerning the public health of the community. They should bear their full part in enforcing its laws and sustaining the institutions that advance the interests of humanity. They should co-operate especially with the proper authorities in the administration of sanitary laws and regulations."

In the Department of Public Health there are at present fifty vacancies. The average salary for a doctor in this department is \$4600, a level that is thirty-ninth on the scale of all the states in the Union. And if you add the territories and cities, we would be about fiftieth. There was a time when we were leading among the state health departments in this country. We are now very much of a borderline state. We have only one physician in the Division of Communicable Diseases, and only one in the Division of Venereal Diseases. With only one exception there is not a medical division or department in which there is a qualified assistant director ready to take over.

The situation is tragic. I have advised the officers of the Society on numerous occasions of the needs of the Department. We have referred to you from time to time our policies and procedures for your advice and endorsement, and have obtained them. I have been informed by the officers from time to time that the co-operation between the Department and the Society is the greatest it ever has been. Sympathy, however, never saved a patient's life. The Society takes pride in having created the Department of Health. It is a dying department, and one that needs prescribing. It needs help.

So far as legislation is concerned, only one bill has been introduced this year, and that has to do with the sanitary code. The help that is needed is not in the appearance formally before a legislative committee, but an action in conference with members of the Ways and Means Committee and with the Governor and his advisers. It is my conviction that unless we can obtain qualified men and unless we can prevent the further depletion of our doctors, we will be faced with a truly critical situation.

The only physicians whom we have been able to employ in the last two or three years are men who have a retirement from the Army or Navy or women who have families and can work part time.

I entered the Department of Public Health in 1938, and to the best of my recollection, I am the last physician to have entered that department who had had any training in public health and who wished to make a professional career of public health. That is how bad the situation is.

The programs that are listed here are, as a matter of fact, in accordance not only with the code of the Society but also with our code of ethics, yours and mine. They are in accord with the program that has been put out by the American Medical Association, which the Executive Committee recommends that you accept, because that is contained in the first portion of this report and reads as follows: "That the trustees of American Medical Association be urged to use all appropriate resources and influences of the Association to the end that complete coverage of the Nation's area and population by local, county, district or regional full-time modern health services be achieved."

I have only one further thing to say. If we lose momentum, the Department becomes impotent, there is only one other thing to do and that is hire substandard men — graduates of unapproved schools and refugees.

No one knows what is going to happen in Washington, but if the Taft Bill or any other similar bill is passed, the Department of Public Health is going to be administering agent here. And if any of you think that even now the Department does not have a truly significant influence on medical practice in Massachusetts, I invite you to come up there for a day and view some of the things that go on.

We want to work with the medical profession. We need your support. We cannot have good public health unless the doctors in Massachusetts support the Department of Public Health.

Committee which relates to this subject. The latter read as follows:

In reviewing this report the Executive Committee gave first consideration to that part of the report submitted by the Subcommittee on School Health. The discussion indicated that this subcommittee came into being as the result of a mandate of the Council which was motivated by a letter that Dr. Fitz received from a committee of school executives asking that the Massachusetts Medical Society set up a committee that would study ways and means of improving medical services in schools. The Executive Committee notes that the subcommittee's principal recommendation is as follows: "To establish an effective liaison between representatives of the Massachusetts Medical Society and education officials at both state and local levels." The Executive Committee is in support of this proposal.

The Executive Committee notes that the subcommittee would activate this idea by (a) having the Massachusetts Medical Society appoint an over-all committee on school medical services and (b) having each district society appoint a local committee on school medical services, it being understood that each district would apply this principle according to the needs of the individual district.

With regard to "a," the Executive Committee recommends that the word "over-all" be deleted and that the word "advisory" be substituted. The Executive Committee is impelled to this action because it believes that the latter word more clearly describes the function of such a committee and the limitations that should govern its activities.

With regard to "b," the Executive Committee, in carrying out the same idea, recommends that the word "advisory" be placed between the word "local" and the word "committee." The Executive Committee also recommends the deletion of the following language, "it being understood that each district will apply this principle according to the needs of the individual district." The Executive Committee is impelled to this action by reason of the fact that it regards these lines as redundant.

The Acting secretary moved the adoption of the first recommendation of the Subcommittee on Public Health, with "a" and "b" as amended by the Executive Committee. This motion was seconded. Dr. Elmer S. Bagnall, Essex North, was recognized. He disapproved of that recommendation of the Executive Committee which would delete as redundant the following language, "it being understood that each district will apply this principle according to the needs of the individual district." He said that he was responsible for this language and that it was purposely used so as to permit the district committees to organize their work in a manner which would suit their individual needs. He moved as an amendment to the motion that this language be permitted to stand. This was seconded. The recommendation of the Executive Committee, subject to Dr. Bagnall's amendment, was adopted by vote of the Council.

The President called the Council's attention to the fact that this report of the Subcommittee on School Health contained thirteen additional recommendations. He said that the Executive Committee recommended that these thirteen recommendations be referred to the advisory committee heretofore authorized for further study and elucidation and that this committee's attention be directed particularly to Recommendations 11 and 12 to the end that the language of these latter recommenda-

tions be changed so as to provide that the interpretation of physical findings shall continue to be the function of the physician alone and not be shared with the school nurse. It was moved and seconded that the recommendations of the Executive Committee with regard to this part of the report be adopted. It was so ordered by vote of the Council.

The President next referred to that part of the report of the Committee on Public Health which referred to public-health personnel. This part imperatively recommended that aggressive support of Dr. Gettling's proposals be given and that the aid of the Committee on Legislation be obtained in expediting his program. The report outlined these proposals as follows:

- (a) To raise the salary level of the professional personnel engaged in public health on a state and local basis
- (b) To institute a sanitary code
- (c) To provide for subsidization of local health departments when, as and if they meet standards as to personnel and program content
- (d) To promote town unions of adequate size (at least 20,000 population) to support a modern public-health and school-health program at a per capita cost of \$1.50 to \$2.50 exclusive of tuberculosis and communicable-disease control and exclusive of garbage collection

The president asked that that part of the Executive Committee report dealing with this subject be read. The Acting Secretary read from the report as follows:

The Executive Committee notes that that part of the report dealing with public-health personnel, if approved by the Council, would commit the Society in a manner in which it should not be committed. It therefore recommends that the Council take no action on this matter on the grounds that the subject is beyond the scope of the Society.

Dr. Roy J. Ward was recognized. He said that he vigorously objected to the conclusion arrived at by the Executive Committee in this matter. The State Department of Public Health, he added, established many years ago largely through the influence of this society, was in danger of losing its efficiency, if not actually breaking down, through its inability to pay salaries to its personnel in keeping with those prevailing in other states or in industry. He pointed out that other states, notably New Hampshire, already had a sanitary code. He said that the recommendations of the Committee on Public Health were in accordance with a request of the American Medical Association. Finally he expressed the thought that the Executive Committee could not have been cognizant of all the facts on this subject when it arrived at its conclusions. Dr. Ward moved the adoption of the recommendations contained in that part of the report of the Committee on Public Health dealing with the subject under discussion. This motion was seconded.

Dr. Elmer S. Bagnall, in speaking in support of the motion, quoted Dr. Lewis H. Bauer, trustee of the American Medical Association, as follows:

expressed the opinion that by setting up a board of trustees the Society would have a small group that would more or less run the organization. Dr Bearse went on to say that the Executive Committee was set up five years ago when the present by-laws were adopted. He added that even then the danger of such a group dominating the Society was thought of and that to prevent such a situation it was provided that no member of the Executive Committee could serve consecutively more than three years.

Dr Edward P. Bagg, Hampden, said that the only question before the Council was the creation of a committee to study this matter. He added that he believed that this recommendation of the Committee on Postwar Planning should prevail.

Dr Frank R. Ober said that he had served as the first chairman of the Executive Committee and that in the beginning this committee was not particularly effective but that this was due to the fact that the duties of the committee had not been defined. He said, however, that as time went on the value of the committee had been proved. Its activities had shortened the Council meetings, and at no time had the Council been a rubber stamp for it. By the same token he believed that the Council would not be a rubber stamp for a board of trustees were such a group set up in the Society. He also pointed out that the recommendation of the Committee on Postwar Planning merely called for a study of this subject.

Dr Root said that his committee, when it made this recommendation, did not have in mind the reducing or minimizing the function of any other committee now in existence. The purpose of the recommendation was simply to find some improved mechanism of meeting the new and varied problems that were continually presenting themselves.

The President said that the question came on the adoption of the recommendation of the Executive Committee and further defined the subject before the Council and asked it to vote on whether or not a special committee should be created to consider the advisability of setting up a board of trustees within the structure of the Massachusetts Medical Society. The Council voted not to establish such a committee.

Dr Root then moved that the Committee on Postwar Planning be discharged. This motion was seconded.

The President said that the Executive Committee in favoring the adoption of this motion also recommended that the discharge carry with it the expression of the Council's gratitude for a job well done and that this expression of gratitude be in a special manner directed toward the chairman, Dr Root, who had given so generously of his time and patience over a period of years. This motion was adopted by vote of the Council. The Council extended a rising vote of thanks to Dr Root and his committee.

Committee to Nominate a Director of Medical Information and Education

(Dr John F. Conlin asked to be excused while this part of the agenda was under consideration. The President granted his request.)

This report (Appendix No. 8) was presented to the Council by the secretary of the committee, Dr Elmer S. Bagnall. The President said that it contained several recommendations: first, that Dr John Francis Conlin be appointed Director of Medical Information and Education; second, that Dr Conlin's employment begin on July 1, 1947; third, that his compensation be at a rate of \$7500 per year, plus ordinary traveling expenses and appropriate vacation periods; that if his services are satisfactory and if he is satisfied with the work as it develops, he shall receive an increase of \$500 on January 1, 1948, and on each January 1 until his maximum salary of \$10,000 will be reached on January 1, 1952; and fourth, that legal counsel should be asked to draw up a written agreement which should embody these general terms, an understanding concerning the mutual termination of the agreement and provisions which will permit adjustments in salary should our national economy become subject to gross inflation.

All these recommendations of the committee were adopted without debate and by the unanimous vote of the Council.

Dr Carl Bearse was recognized. He commented on the fact that the Council had just created a position without any statement regarding the duties of this position. He moved that the Director of Medical Information and Education be assigned to the Office of the Secretary. Dr Donald Munro raised as a point of order that this motion constituted new business and was therefore out of order. The President declared the point of order well taken.

(At this point, Dr John F. Conlin, having returned to the meeting, was asked to stand. He was greeted with applause.)

Dr Ober moved that the committee report as a whole be accepted and that the committee be discharged with the thanks of the Council. This motion was seconded, and it was so ordered by vote of the Council.

Committee on Postgraduate Assembly

This report, which is as follows, was presented by the chairman, Dr Leroy E. Parkins, Suffolk.

The committee invited the other New England state medical societies to co-operate in presenting the New England Postgraduate Assembly; each society responded and appointed members to the Executive Committee. A Program Committee and other committees were appointed, and the Assembly was presented at the Hotel Bradford on October 30 and 31, 1946.

The attendance was as follows:

Maine	40-
New Hampshire	30
Vermont	16

The motion was adopted by vote of the Council

Committee on Postwar Planning

Dr Howard F Root, Suffolk, chairman, presented this report (Appendix No 7) Dr Root moved the acceptance of the report This motion was seconded, and it was so ordered by vote of the Council The report reviewed the accomplishments of the committee It indicated that the committee regarded its work as finished It expressed the belief that certain of its subcommittees should be continued as special committees. With the latter in mind, Dr Root moved that the Council authorize the creation of a special committee to be known as the Committee on Postgraduate Medical Education, that this committee consist of seven members to be appointed by the President subject to confirmation by the Council, and that the committee so appointed be charged with the direction of the Society's postgraduate educational program and its Bureau of Clinical Information, except as might be otherwise ordered by the Council This motion was seconded, and it was so ordered by vote of the Council

Dr Root moved that the Council authorize the creation of a special committee to be known as the Committee on Medical Economics, that this committee consist of five members to be appointed by the President subject to confirmation by the Council, and that the committee so appointed be charged with the study and direction of methods by which members of the Society might be informed regarding the economic status of medical practice now and in the future This motion was seconded, and it was so ordered by vote of the Council

Dr Root moved that the Council authorize the creation of a special committee to be known as the Committee on Veterans Affairs and that the members of this committee be appointed by the President subject to confirmation by the Council This motion was seconded, and it was so ordered by vote of the Council

Dr Root moved that the Council authorize the creation of a special committee of five members to be appointed by the President, subject to confirmation by the Council, to consider the advisability of setting up a board of trustees within the structure of the Massachusetts Medical Society and that in the event that such a committee decides affirmatively in this matter it be further charged with recommending the duties of such a board of trustees and with the preparations of such amendment or amendments to the by-laws as might be necessary

The President said that the Executive Committee had concerned itself with this recommendation He asked the Acting Secretary to read that part of that committee's report which dealt with this subject The latter read as follows

The Executive Committee recommends that the Council disapprove this recommendation In the discussion attend-

ing this subject, it came out that the Executive Committee, consisting of one representative from each district in the Commonwealth, had been performing what might be regarded as the functions of a board of trustees, but that there was a feeling in the Committee on Postwar Planning that there was at times a lack of over-all policy due to the size of the Executive Committee and the shortness of time (three years) in which any single member might hold continuous office On the other hand it was emphasized in this discussion that there never had been any difficulty in getting the Executive Committee together even in emergency session and that a board of trustees might result in too centralized a government, which might affect unfavorably the democratic character of the Society and alienate the interests of the ordinary member The wisdom of setting up a board of trustees, which in the ordinary course of events might be expected to take over the functions now being satisfactorily performed by the Executive Committee, was seriously questioned It was pointed out that the recommendations did not actually propose that such a board of trustees be set up, but only that a committee be authorized to study this subject It was also pointed out that a board of trustees might be needed to give direction to the efforts of the Director of Medical Information and Education There were certain district societies that reported their councilors, as unanimously opposed to the proposal

The Acting Secretary moved the adoption of the recommendations of the Executive Committee. This motion was seconded

Dr Bagnall was recognized He said that he spoke as an ex-president He expressed the thought that only the individual who has served as president quite comprehends the whole prospective of the structure of the Society He said that there was need for a group in the Society to whom the President could look for advice with regard to policies He said that his experience as president led him to believe that the Executive Committee did not fill this function Theoretically, he said, the setup of the Executive Committee was excellent He said that it had not worked out because of the lack of interest which many of the members of the committee took in its proceedings He said that he did not necessarily favor a board of trustees with any great powers, what he did want was a policy committee with a continuity of interests and made up of faithful, self-sacrificing men with the service motive to whom the President could turn for advice He pointed out that the recommendation of the Committee on Postwar Planning simply asked for a committee to study this matter Dr Leroy E Parkins, Suffolk, seconded Dr Bagnall's remarks

Dr George L Schadt, Hampden, said that a board of trustees would make the necessity for an executive committee practically nil He said that presumably such a board might be made up of five or seven members He added that he did not like to see such power placed in a small group He thought that the answer to this whole difficulty might be had by reducing the size of the Council so that each member would represent one hundred members rather than twenty, as now prevails

Dr Carl Bearse, Norfolk, stated that he thought that the Society had done very well over the years without a board of trustees He added that as the Society is set up today it is truly democratic He

Second, that this rate become effective January 1, 1948, and

Third, that of the total dues, \$5 00 be earmarked for the use of the Boston Medical Library

Dr George L. Schadt, Hampden, moved the adoption of the first recommendation. This motion was seconded.

Dr William H. Blanchard, Suffolk, thought that by raising the dues the Society might lose certain of its members. In consequence of that he said that there was some question in his mind whether or not the raising of the dues would really provide the funds necessary to do the things set forth in the committee's report.

Dr Schadt said that in increasing the dues the individual member should think of this increase as enabling the Society to better serve the public rather than in terms of what additional benefits should accrue to him. He added that he was for the increase and that even if it were greater he would still support it.

Dr Hyman Morrison, Norfolk, asked if the committee had considered the point of view of the young man who had just graduated and of the man in declining years whose income is waning. The President replied that there was no mention of such in the report.

The first recommendation of the Executive Committee was adopted by vote of the Council.

The President said that the second recommendation of the Executive Committee, namely, that the new rate of dues become effective on January 1, 1948, was before the Council. Its adoption was moved and seconded. The motion was adopted by vote of the Council. The adoption of the third recommendation of the Executive Committee was moved and seconded.

Dr Phippen was recognized and spoke as follows:

I ask your indulgence to say a few words about the Boston Medical Library. It is an old institution, founded in 1805. It had many vicissitudes, and in 1872 the Massachusetts Medical Society, having a library of its own, suddenly decided that it did not need it and transferred its collection of books to the Boston Public Library.

This created one of our customary furores in the Society, and a lot of younger men started the Boston Medical Library, which began in Hamilton Place in 1875 and which has grown to this large establishment that we have today. It is now the third largest medical library in the country. It has nearly 200,000 books — probably over that now — and 135,000 pamphlets. It has a large collection of rare books.

The Boston Medical Library should fill a definite place in the profession of medicine, not only in Boston and in Massachusetts but also in all the New England states. It is one of the most important parts of the practice or of the profession of medicine.

I have often heard it said that those of you in the distant parts of the Commonwealth do not use the Library. That is not a fact. Every time you read one of the papers that are published in the *New England Journal of Medicine*, which have made the *Journal* what it is today, you are using the Library. All the bibliography for those papers comes out of this library. So every one of you use it.

A medical library occupies the same relation to the profession of medicine that a public library occupies to the citizens of a community. A lot of citizens in the community do not use the public library, and yet they pay for

it and they pay for it gladly, because they know it has to do with their educational development. The same thing is true of the Boston Medical Library. You ought to be glad and willing to help support the Library because of the good it does to the profession at large.

A survey of the Library made by Dr Fleming, of the Medical Library of Columbia University, in 1941 developed the fact that this library should be a real reference library, co-ordinating its activities with the libraries of the medical schools and with the libraries of the hospitals. And a committee that was formed to review that report so recommended. The trustees of the Library have tried hard to bring that about, but unfortunately it could not be done because of lack of funds. The Library depends for its income on certain gifts and bequests and on the income from its members. Many well intentioned people have given money to the Boston Medical Library, but unfortunately, a great deal of that money is earmarked for rare and unusual books. Therefore that money cannot be used for the running expenses of the Library. Every effort has been made by the Board of Trustees, particularly by Dr Cheever, to interest philanthropic organizations in the Library. Foundations have been approached to see if they would contribute funds, but they are not interested in an organization that is not a going concern.

The trouble with the Library is that it has outgrown its income. It has gone on successfully and wonderfully, really, with the amount of help that it has had, to give the service that it has given, but it does not by any means begin to give the service that it ought to give. When you come to think that here is a library worth a great deal of money, with 200,000 odd volumes of books, that is serviced by a director, a secretary and four employees only, you can understand why it cannot give service.

This library could give a tremendous amount more service than it gives at the present time if it had the proper income. The income of the Library today is only about \$30,000, and at that the yearly deficit is about \$1000 or a little more. With the income that the Massachusetts Medical Society could give us, we would be able to service the Library. We would be able to provide enough personnel to put the multitudes of books that line the corridors, the cellars, the attic and the garret on the shelves where they belong, and to provide sufficient help so that you could use these books when you wanted them.

The Library is educational. I want to call your attention to this painting [pointing to the picture behind the President's desk] by an anonymous donor, which has been redone and which was exhibited at the Ether Day Celebration of the Massachusetts General Hospital, it caused a great deal of interest to everybody. It is one of the educational features of the Library.

I shall be only too glad to answer questions as to the needs of the Library, but I can say frankly that, unless something is done to help the Library, it will go on functioning in this modest way — for how long I cannot tell. You are economists enough to know that if it spends \$1000 a year more than it earns with an annual income of only \$30,000 a year, it will not be long before the Library will have to close its doors.

All I can say is what Dr. Warren said on this occasion [again pointing to the picture], "Gentlemen, this is no humbug."

Dr Schadt asked the previous speakers that in the event that the recommendation before the Council were adopted whether the Library would devise some method by which physicians in the western and northern parts of Massachusetts would be sent such books as they may require. Dr Phippen answered in the affirmative.

Dr Bearse asked whether it would still be necessary for the Library to have its own membership and dues if the motion prevailed. Dr Phippen answered the question as follows:

Yes, it will be. Some of you may remember that a number of years ago an attempt was made to form an

Massachusetts	359
Rhode Island	21
Connecticut	22
	<hr/> 488
The income and expenses were as follows	
Receipts from exhibits	\$3,600 00
Receipts from registrations and tickets	3,202 45
	<hr/>
Total	\$6,802 45
Expenses	5,964 97
	<hr/>
Credit balance	\$837 48

This credit balance will offset deficits made in previous years. It also demonstrates that the Assembly can be self-supporting.

The Assembly Executive Committee recommends that the New England Postgraduate Assembly be continued as a permanent independent organization sponsored and supported by the New England state medical societies. It was suggested that a governing board be composed of officially appointed representatives from all the medical societies, each being allowed one representative for each one thousand members or fraction thereof (this is essentially the ratio of the current organization). Financial support, if necessary, would likewise be on a percentage basis.

The committee recommends that a committee be appointed to arrange an assembly in 1947 and that the Council approve of the setting up of an independent organization to be known as the New England Postgraduate Assembly.

Dr Parkins moved the acceptance of the report. The motion was seconded and it was so ordered by vote of the Council. Dr Parkins said that the report contained two recommendations, first, that a committee be appointed to arrange a postgraduate assembly in 1947. He moved the adoption of the first recommendation. This motion was seconded, and it was so ordered by vote of the Council. He said that the second recommendation requested the Council to approve the setting up of an independent organization to be known as the New England Postgraduate Assembly. He moved the adoption of this recommendation. This motion was seconded by a counselor.

The President said that the Executive Committee considered this and that inasmuch as the Council of the New England State Medical Societies was a going concern in which the Society was represented it thought that if the sponsorship of the postgraduate assembly was to pass from the Massachusetts Medical Society to New England it was desirable that it be assumed by this council as the only organization that is truly representative of New England as a whole. The President stated that at the time of the meeting of the Executive Committee, inasmuch as this subject had not been presented to the Council of the New England State Medical Societies, its viewpoint had not been ascertained. He added that it came to the committee's attention that this council was to meet on January 15. The Secretary, who is one of the representatives of the Society in this council, was instructed to ascertain its views in this matter. The President added that the Secretary had followed the instructions and that the viewpoint of the New England Council in

this matter was fully outlined in the report of the Executive Committee. He said that this report indicated that the New England Council would have to ascertain the view of the several individual state societies which it represents before it could express an opinion with regard to the proposition. The report indicated that this could not be done much before June 1 and that this would be too late to allow for the planning of an assembly in the fall of 1947. The President said that as a result of this the Secretary suggested that the Council approve the first recommendation, which it had already done, so as to provide for the continuation of the assembly, and lay the second on the table until such time as the Council of the New England State Medical Societies was ready to act.

Dr Frank R. Ober moved that the second recommendation be laid on the table. The motion was seconded by Dr. Walter G. Phippen, Essex South. It was so ordered by vote of the Council.

Committee to Study Increase in Assessment of Dues

This report (Appendix No. 9) was offered by the chairman, Dr. Frank R. Ober, Suffolk, who moved its acceptance. This motion was seconded, and it was so ordered by vote of the Council.

Dr. Ober said that in connection with an increase in dues the committee had considered certain functions of the Society which it ought to be, but was not, serving. He said that there was the matter of a retirement fund spoken of earlier in the meeting, as well as the care of widows and orphans of physicians who might find themselves in difficult circumstances. He said that the Vermont State Medical Society sets aside part of its annual dues for this purpose. Dr. Ober spoke of the Massachusetts Benevolent Society and the aid that it was giving to many. He said that thought should be given to the matter of combining in some way the efforts of this organization with those of the Massachusetts Medical Society. He said that the Boston Medical Library should be helped. He finally said that, although his committee offered no definite recommendations at this time, it was hoped that the Council would be thinking about the matter contained in the report. He said that the Executive Committee in its analysis of the report offered certain recommendations with regard to the matter of dues. He asked that these recommendations be read.

At the direction of the President, the Acting Secretary read from the report of the Executive Committee as follows:

With all these considerations in mind [referring to the Executive Committee's analysis of the report] the Executive Committee believes the membership dues should be increased. It also believes that out of this increase a certain allotment should be made to the Boston Medical Library. It therefore recommends:

First, that the Council set the membership dues at \$25.00 per year,

Dr Watkins moved its acceptance. This motion was seconded, and it was so ordered by vote of the Council.

Committee to Study Income Level for Blue Shield

This report, which is as follows, was presented by the chairman, Dr Charles F Wilinsky, Suffolk.

The committee has met to study the income level for Blue Shield subscribers in relation to eligibility for the Ward Plan.

It has considered this question carefully and has given justifiable and serious thought to the relation of income level for medical eligibility under the Blue Shield Plan as related to similar eligibility to Blue Cross Ward Plan Service.

The Blue Cross has recently given consideration to a change in income limitations for eligibility for its Ward Plan and has approved the following levels:

Single subscriber, no dependents	\$2 000
Subscriber and one dependent	2 500
Subscriber with more than one dependent	3,000

A canvass of our committee has resulted in accord and approval of the above-mentioned earning limits in relation to Blue Shield eligibility, and we so recommend the above schedule for the consideration of the Council.

The President said that the Executive Committee was much confused by this report and recommended that it be referred back to the committee for elucidation. He called on Dr Wilinsky to clarify it.

Dr Wilinsky said that this matter had been referred to his committee for the purpose of determining whether or not, in view of the higher cost of living, the worker earning \$2000 a year or the family whose total income was \$2500 was in as good a position to pay a supplementary fee to the surgeon as he was when the Blue Shield was established. He said his committee believed that they were not. Consequently, it recommended the following new schedule: that no supplementary fee should be paid to the surgeon by the person earning \$2000 or less, by the person with one dependent earning \$2500 or less, or by the person with more than one dependent earning \$3000 or less. Dr Wilinsky moved the adoption of the recommendation of his committee. This motion was seconded, and it was so ordered by vote of the Council.

Committee to Meet with General Hawley

In the absence of Dr McCarthy, the report was presented by the President. This report is as follows:

Your committee has been to Washington, has completed Part A of the Fee Schedule and has turned it over to the Massachusetts Medical Service, Blue Shield, to administer.

The President, by way of implementing this report, said that the contract between the Veterans Administration and the Blue Shield had been signed. He added that the contract was in accordance with all the votes of the Council as to fees. It was moved and seconded that the report be accepted. It was so ordered by vote of the Council.

Medical Advisory Committee to the Regional OPA

This report, which is as follows, was presented by the chairman, Dr Joseph Garland, Suffolk.

The Medical Advisory Committee to the OPA has nothing more to do now than to review an occasional sugar application. When sugar goes off rationing the committee can be reured and we will be glad of the chance.

It was moved and seconded that the report be accepted. It was so ordered by vote of the Council.

Committee on Industrial Health

This report, which is as follows, was offered by the chairman, Dr Daniel L. Lynch, Norfolk, as a report of progress.

At the present time the Committee on Industrial Health can submit only a report of progress as follows:

First, a survey is in progress to ascertain the names and connections of the physicians in Massachusetts who are actually engaged in industrial medicine, that is, physicians who have a definite connection with an industrial, mercantile or other establishment.

Second, we are taking steps to determine the number and connections of nurses who are employed in industrial, mercantile, business or similar establishments.

Third, we are taking steps to determine the number of nurses who have medical supervision and those who do not.

It is our hope that this survey will be well along by the February meeting.

He moved its adoption as such. The motion was seconded, and it was so ordered by vote of the Council.

APPOINTMENTS

The President made the following *ad interim* appointments:

To the Committee on Legislation

Dr Solomon L. Skvirsky, Norfolk

To the Committee on Cancer

Dr Shields Warren, Suffolk, *Chairman*

To the Committee on Veterans Affairs

Dr Edwin M. Mahoney, Hampden

Dr Charles A. Wheeler, Worcester North

It was moved and seconded that these appointments be confirmed. It was so ordered by vote of the Council.

NEW BUSINESS

Dr Augustus Thorndike, Suffolk, was recognized. He submitted the following resolution:

WHEREAS, The Fracture Committee of the American College of Surgeons has recommended the establishment of community rehabilitation centers in all states, and

WHEREAS, The National Service Fund of the Disabled American Veterans is sponsoring the establishment of a nonprofit organization in Boston to be called the Rehabilitation Center, on an outpatient service basis for patients in the terminal stages of convalescence, to which may be referred by doctors, by hospitals and by governmental and private agencies veteran and civilian patients with disabilities requiring medical evaluation and treatment, including physical therapy and occupational therapy, as well as evaluation for proper job placement at time of release, be it therefore

RESOLVED, That the Council authorize the president to refer to the appropriate committee or committees for study, with a report and a recommendation to be presented at the next meeting of the Council, the question whether there

academy of medicine, a combined membership of the Library and the Massachusetts Medical Society, and at that time it was found to be absolutely impracticable from a legal point of view

The corporate body of the Library must remain in its fellowship, and its board of trustees. To change that or to change the name of the Library would create an insurmountable legal controversy. I have been into that with legal counsel, and the trouble is that many of these bequests are left for specific purposes and that to change the name of the Library, everyone, not only the families of the donors but those who might be interested in the ultimate distribution of the property, would have something to say. Such a legal tangle would be insurmountable. The membership of the Library must remain the same so far as the corporate interest is concerned.

Dr Norman A Welch, Norfolk, asked if the legality of the recommendation had been inquired into. Dr Phippen read as follows from a letter that he had received from Mr Robert Dodge, counsel for the Library and also for the Massachusetts Medical Society:

I think that the Massachusetts Medical Society may lawfully agree to contribute \$25,000 a year toward the support and maintenance of the Boston Medical Library. Such an expenditure would seem plainly to be in the interests of the preservation of health, and therefore come within the chartered purposes of the Society.

Dr Ober pointed out there might come a time when the Library might not need the funds that the adoption of this recommendation would provide and that under such circumstances the action proposed by the recommendation could be modified or rescinded entirely.

Dr Nicholas Scarcello, Worcester, asked if it would be proper to amend the recommendation of the Executive Committee so as to provide that this grant to the Library of \$5 00 from each \$25 00 carry with it a request that the Boston Medical Library make the members of the Massachusetts Medical Society associate members of the Library. Dr Phippen said that although he could not speak with authority on the subject, he thought that something like this could be done. The President said that he would entertain Dr Scarcello's amendment.

Dr Hyman Morrison thought that such an arrangement would tend to lessen the income that now accrues to the Library from dues.

Dr Fremont-Smith, in seconding Dr Scarcello's amendment, said that unless some arrangement of this kind could be made the Council would be criticized by the men in the outlying districts. He added that he rather favored the idea of making this grant to the Library contingent on the Library entering into some such agreement.

The President said that he doubted that the Library would ignore the request contained in the amendment. He announced that the question before the Council was the adoption of the third recommendation of the Executive Committee as amended by Dr Scarcello. It was so ordered by vote of the Council. Dr Ober moved the adoption of the report as a whole as amended. This motion was seconded, and it was so ordered by vote of the Council.

Report on the December, 1946, Meeting of the House of Delegates of the American Medical Association

The report (Appendix No 10) was presented by Dr. David D Scannell, Norfolk. The President, in commenting on its excellence, said that it was informational only. The acceptance of the report was regularly moved and seconded. It was adopted by vote of the Council.

Committee to Survey Malpractice Insurance

This report, which is as follows, was submitted by the chairman, Dr Carl Bearse, Norfolk:

A meeting of the committee was held on October 2, 1946. It was voted that letters be sent to the following insurance companies underwriting most of the medical malpractice insurance in Massachusetts, secretaries of all state medical societies in the United States, and all members of the Massachusetts Medical Society, together with a questionnaire to be completed:

The letter to the insurance companies inquired as to the number of physicians insured by them in Massachusetts, the number of Massachusetts Medical Society members insured, whether they accepted graduates of unapproved medical schools, the amount of money paid out in settlement of claims during the previous ten years, the largest sum paid in the settlement of a single claim, their coverage and rates, and whether they would co-operate with a committee of the Massachusetts Medical Society by informing them of all suits or threats of suits brought against members of the Society insured by them for the interchange of opinion, provided of course that the physician insured agreed to this.

The letter sent to the secretaries of all state medical societies informed them that the Massachusetts Medical Society was making a survey of malpractice insurance in this state and that the Society would like to know how other state societies concerned themselves with this problem. The specific inquiries addressed to them were as follows: Does your society defend its members against suits of malpractice? Does your society pay any indemnity? Do you have a committee to serve as a clearing house for all suits for malpractice? What rates are charged by insurance companies in your state?

The letter and questionnaire sent to all members of the Massachusetts Medical Society are not being repeated here since they have already been mailed to every fellow. Replies are still coming in and are being tabulated for study.

This report is purely informational and is submitted as one of progress.

Dr Bearse moved the acceptance of the report. This motion was seconded, and it was so ordered by vote of the Council.

Committee on Physical Medicine

This report, which is as follows, was presented by the chairman, Dr Arthur Watkins, Middlesex South:

No new business has been brought before this committee, but the following informational report is submitted. In view of the several substandard schools for training physical therapists in this area, it is thought worth while to inform members of the Massachusetts Medical Society that there is available a printed directory of graduates of physical therapy schools approved by the American Medical Association who are members of the Massachusetts Physiotherapy Association. Physicians will be protecting their own and their patients' interests when prescribing physical therapy if technicians carrying out the orders have had training with the high medical standards required of this group. These directories can be obtained from Mrs Dorothy V Warren, Physical Therapy Department, Massachusetts General Hospital, Boston 14.

APPENDIX NO 2

REPORT OF THE EXECUTIVE COMMITTEE OF THE COUNCIL

The Executive Committee of the Council met on January 8, 1947, in Sprague Hall, 8 Fenway, Boston, Mass., at 4 00 p m. Dr Dwight O'Hara, president of the Massachusetts Medical Society, presided. This was a regular pre-Council meeting called for the purpose of processing committee reports and for such other business as might legally come before it.

The record of the last meeting as submitted by the Secretary was approved.

Committee Reports

Report of the Meeting of the House of Delegates of the American Medical Association held in Chicago on December 7, 8 and 9, 1946

This report was submitted by Dr David D Scannell. The Executive Committee commends this report for the clarity with which it outlines the proceedings of the House of Delegates, it looks on it as informational only and recommends that the Council adopt it as such.

Committee on Arrangements

The Executive Committee notes that this report is informational only and recommends its adoption by the Council.

Committee on Publications

The Executive Committee notes that this report contains two recommendations.

The first request is that the Council authorize the publication of a directory of the officers and fellows of the Massachusetts Medical Society during the year 1947 and that the sum of \$2000 be appropriated for this purpose. The Executive Committee notes that this appropriation is provided for in the budget. The Executive Committee recommends that the Council adopt this recommendation.

The second recommends that the advisability of adopting some sort of retirement plan for the full-time employees of the Society be referred to either an existing committee or a specially appointed committee to the end that if such committee thinks that action is advisable it be empowered to present such a retirement plan to the Council. The recommendation further provides that, in the event that a plan is recommended to the Council it must first have the approval of the Committee on Finance. The committee's report explains that because of the scientific character of the Society its employees may not participate in the benefits of the present Social Security Act. The Executive Committee recommends that the Council adopt this recommendation and that this subject be referred by the President to the committee which has recently studied and reported on salary adjustments for the employees of the Society.

Committee on Public Relations

This report recommends that the Council authorize the Committee on Public Relations to establish a speakers' bureau. The Executive Committee concurs in this recommendation.

The discussion on this subject before the Executive Committee brought out several facts all of which pointed to the wisdom and necessity of establishing such a bureau. The President and Secretary spoke of the many requests that they receive from time to time from lay organizations requesting speakers on medical and medicoeconomic subjects and of their inability to find those willing to accept such assignments. They both felt that in failing to do something about this in the past, the Society has neglected a valuable means of improving its public relations.

Reference was made to the fact that the American Medical Association had established a speakers' bureau as a means of making the people as a whole more aware of what organized medicine is offering in the interest of the public good. This national bureau will be in a position to train groups of doctors from the various states from the standpoint of adequately informing them not only on the subjects to be discussed but also on the methods of approach likeliest to succeed.

The Committee on Public Relations asks the privilege of organizing this movement in the Society. It would make its selection of speakers from all parts of the state. The Executive Committee also believes that by adopting this recom-

mendation the Council would give at least some direction to the office of the Director of Medical Information and Education and that this office might as one of its duties work with and under the direction of the Committee on Public Relations in setting up and supervising the bureau called for in this recommendation.

Committee on Legislation

The Executive Committee regards this report as informational only and recommends its adoption as such.

Committee on Finance

This report presents the budget for the year beginning January 1, 1947. The Executive Committee recommends the adoption of the budget as presented by the Committee on Finance.

Report of the Committee on Society Headquarters

This report takes notice of the poor state of the Society's mechanical office equipment and of its inadequacy in meeting the demands put on it. The Executive Committee points out that the moneys necessary to carry out the recommendations contained in this report are incorporated in the budget as submitted. The Executive Committee recommends the adoption of the recommendations contained in this report.

Committee on Public Health

In reviewing this report the Executive Committee gave first consideration to that part of the report submitted by the Subcommittee on School Health. The discussion indicated that this subcommittee came into being as the result of a mandate of the Council which was motivated by a letter that Dr Fitz received from a committee of school executives asking that the Massachusetts Medical Society set up a committee that would study ways and means of improving medical services in schools. The Executive Committee notes that the subcommittee's principal recommendation begins as follows: "To establish an effective liaison between representatives of the Massachusetts Medical Society and educational officials at both state and local levels." The Executive Committee is in support of this proposal.

The Executive Committee notes that the subcommittee would activate this idea by (a) having the Massachusetts Medical Society appoint an over-all committee on school medical services, and (b) having each district society appoint a local committee on school medical services, it being understood that each district would apply this principle according to the needs of the individual district.

With regard to "a," the Executive Committee recommends that the word "over-all" be deleted and that the word "advisory" be substituted. The Executive Committee is impelled to this action because it believes that the latter word more clearly describes the function of such a committee and the limitations that should govern its activities.

With regard to "b," the Executive Committee in carrying out the same idea, recommends that the word "advisory" be placed between the word "local" and the word "committee." The Executive Committee also recommends the deletion of the following language: "it being understood that each district will apply this principle according to the needs of the individual district." The Executive Committee is impelled to this action by reason of the fact that it regards these lines as redundant.

The Executive Committee notes that this report contains thirteen additional recommendations. Although it expresses its sympathy with what it conceives as the idea behind most of these recommendations, it recommends that they be referred to the advisory committee heretofore proposed by this report for further study and elucidation when and if such a committee is set up. The Executive Committee is impelled to this action because of the magnitude of the recommendations and because certain practical questions are in need of answer before the Council should commit itself.

In referring these remaining recommendations to the proposed advisory committee the Executive Committee suggests that the Council specifically direct the attention of such an advisory committee to recommendations 11 and 12, to the end that the language of these recommendations be changed so that the interpretation of physical findings

is need for such a community rehabilitation center and service in Boston, organized in accordance with the *Report of the Baruch Committee on Physical Medicine*

The President referred this resolution jointly to the Committee on Rehabilitation and the Committee on Industrial Health

At this point in the meeting, Dr Daniel B Reardon, Norfolk South, said that because he was late in entering the meeting he did not know whether or not any action had been taken by the Council regarding Dr Tighe's illness. The President replied that in opening the meeting he had acquainted the Council with the fact that Dr Tighe was ill. He added that he talked with him over the telephone that morning, that the latter's spirits seemed good and that he expected to be around again shortly. The President said that a box had been placed in the hall outside the Council room for the benefit of all those who wished to participate in sending the secretary a modest and appropriate remembrance.

The President announced that there was no further business before the Council. It was moved and seconded by vote that the Council adjourn.

The president announced the Council adjourned at 120 p m.

MICHAEL A TIGHE, *Secretary*

APPENDIX NO 1

ATTENDANCE OF THE COUNCILORS

BARNSTABLE

P P Henson
C H Keene

BERKSHIRE

I S F Dodd
C F Kernan
H M Scoville
P J Sullivan

BRISTOL NORTH

W H Allen
M E Johnson
C B Kingsbury
W J Morse
J L Murphy
W M Stobbs

BRISTOL SOUTH

R B Butler
J C Corrigan
C C Trapp

ESSEX NORTH

E S Bagnall
R V Baketel
G J Connor
N F DeCesare
H A Fenton
H R Kurth
P J Look
R C Norris
G L Richardson
F W Snow

ESSEX SOUTH

R E Foss
Loring Grimes
C A Herrick

P P Johnson

B B Mansfield

O S Pettingill

W G Phippen

J R Shaughnessey

H D Stebbins

P E Tivnan

C F Twomey

C A Worthen

FRANKLIN

F A Millett

HAMPDEN

E P Bagg
A J Douglas
E C Dubois
Frederic Hagler
G D Henderson
A G Rice
G L Schadt

HAMPSHIRE

H A Tadgell

MIDDLESEX EAST

Robert Dutton
W H Flanders
R W Layton
K L MacLachlan
M J Quinn
W F Regan
R R Stratton

MIDDLESEX NORTH

R L Drapeau
A R Gardner
W F Ryan
W L Twarog

MIDDLESEX SOUTH

E W Barron
J M Barv
J D Bennett
G F H Bowers
Alice M Broadhurst
Madelaine R Brown
R N Brown
R W Buck
E J Butler
J F Casey
C W Clark/
J A Daley
C L Derick
J G Downing
C W Finnerty
H Q Gallupe
V A Getting
H G Giddings
H W Godfrey
A D Guthrie
Eliot Hubbard, Jr
F R Jouett
A A Levi
A N Makechnie
Dudley Merrill
C E Mongan
J P Nelligan
Dwight O'Hara
Fabyan Packard
L G Paul
L S Pilcher
Max Ritvo
M J Schlesinger
K J Tillotson
A B Toppan
J E Vance
C F Walcott
A L Watkins
Hovhannes Zovickian

NORFOLK

A A Abrams
C E Allard
B E Barton
Carl Bearse
Joseph H Carey
J H Cauley
Susannah Friedman
D L Halbersleben
J B Hall
H B Harris
R J Heffernan
P J Jakmauh
C J E Kickham
D L Lionberger
D S Luce
C M Lydon
D L Lynch
R T Monroe
F J Moran
Hyman Morrison
D J Mullane
J J O'Connell
W R Ohler
G W Papen
H A Rice
S A Robins
D D Scannell
S L Skvirsky
E C Smith
Kathleyn S Snow

NORFOLK

A R Staggs
J P Treanor, Jr
N A Welch
E T Wyman

NORFOLK SOUTH

D L Belding

Harry Braverman
Frederick Hinchliffe
E K Jenkins
N R Pillsbury
D B Reardon
H A Robinson
R G Vinal

PLYMOUTH

J C Angley
H H Hamilton
P H Leavitt
G A Moore
B H Pearce

SUFFOLK

H L Albright
A W Allen
W H Blanchard
W J Brickley
W E Browne
A M Butler
A J A Campbell
David Cheever
J F Conlin
Pasquale Costanza
N W Faxon
Reginald Fitz
Maurice Fremont-Smith
Channing Frothingham
Joseph Garland
John Homans
L M Hurxthal
H A Kelly
T H Lanman
R I Lee
C C Lund
Donald Munro
R N Nye
F R Ober
F W O'Brien
J P O'Hare
L E Parkins
L E Phaneuf
Helen S Pittman
W H Robey
H F Root
R M Smith
Augustus Thorndike
J J Todd
Conrad Wesselhoeft
C F Wilnsky

WORCESTER

C R Abbott
A W Atwood
George Ballantyne
I J Cohen
E J Crane
J M Fallon
L M Felton
R H Goodale
J A Lundy
D K McClusky
J M Olson
F A O'Toole
R S Perkins
E L Richmond
N S Scarcello
R F Sullivan
G C Tully
R J Ward
B C Wheeler

WORCESTER NORTH

H C Arcey
J J Curley
C B Gay

As touching on the necessity of increasing the dues, the Treasurer, Dr Eliot Hubbard, Jr., submitted the following

For basic comparison the income for 1946 was as follows

Annual dues	\$51,522
Nonresident dues	1,776
General Fund	5,162
Phillips Fund	250
Censors' fees	1,185
Profit (Committee on Arrangements)	5,301
Profit (Postgraduate Assembly)	835
	<hr/>
	\$66,031

Income from the *Journal* is not included as it is not a constant sum, nor certain as a future source

Taking the same income figure for 1947 and the budget estimate for 1947 of \$64,195, there would only be a clearance of \$1,836. This would not take care of the proposed salary of the Director of Medical Information and Education, to say nothing of other proposed and worthy expenditures. Therefore, some increase in dues is necessary.

In considering the increase in dues in the light of new and proposed expenses, it must be remembered that the increase applies only to annual dues, not to nonresident dues.

It has been advocated that the annual dues be increased to \$25.00 and that \$5.00 of this be allocated toward support of the Boston Medical Library. If this was done, the income and expense accounts would be as follows

<i>Income</i>	
Annual dues (200 resident fellows)	\$150,000
Other income	14,509
	<hr/>
Total	\$144,509
<i>Expenses</i>	
Budget	\$64,195
Boston Medical Library	26,000
Ultimate salary of Director of Medical Information and Education	10,000
	<hr/>
Total	\$100,195
Credit balance	\$44,314

If the dues were increased to \$20.00, the income and expense account would be as follows

<i>Income</i>	
Annual dues	\$104,000
Other Income	14,509
	<hr/>
Total	118,509
Estimated expenses	100,195
	<hr/>
Credit balance	\$18,314

This might seem adequate at the moment, but other projects are being proposed, namely, a retirement fund for the full-time personnel in the administrative office, a fund to aid and assist member physicians incapacitated through illness, injury or age, and like aid for needy widows and orphans of members. With these in mind and the annual increase in administrative expense that has occurred regularly over many years, it might not be long before the dues would have to be increased to \$25.00 from \$20.00, if the latter figure were now agreed on. If the annual dues be raised to \$25.00, I should like to make the following suggestions

That the refund to district societies be increased from \$4,000 a year to \$8,000
That the total amount of the assets of the General Fund be set at some figure agreed on by the Committee on Finance, perhaps \$250,000, and not be increased each year by reinvestment of surplus, as is up to now possible and customary for no specific purpose, and that in any given year, after running expenses have been paid and aid to the Boston Medical Library and other beneficiaries given, the balance of income over expenditures be automatically turned over to the Building Fund. This fund so augmented would assure the purchase of adequate headquarters at the proper time and would allow for a Building Fund endowment, the income from which would support the running of this establishment

Dr Walter G. Phippen, a member of the Executive Committee and president of the Boston Medical Library, made a statement as to the needs of the Library, which was in much the same vein as previously reported to the Council by the Executive Committee. He said that if the Library had an additional income of \$25,000 to \$30,000 yearly, it could become a very valuable instrument to all the physicians of the Commonwealth. He said he realized that the Library was not doing the job that it should. He explained this by saying that it did not have sufficient funds. He added that it was his feeling that the Library occupies a position toward the profession of medicine in Massachusetts exactly the same as that occupied by a public library toward the taxpayers of the community.

In response to a question, Dr Phippen said that with additional funds available with which to sort and catalogue books, which were at present piled up in many places, more space, to the extent of two or more large rooms, might be made available for the use of the Society. The discussion also brought out the fact that if funds were made available to the Library, it could send books to any member of the Massachusetts Medical Society and therefore be of service to all.

With all these considerations in mind, the Executive Committee believes the membership dues should be increased. It also believes that, out of this increase, a certain allotment should be made to the Library. It therefore recommends

That the Council set the membership dues at \$25.00 per year

That the rate become effective January 1, 1948

That of this \$25.00, \$5.00 be earmarked for the use of the Boston Medical Library

Committee Surveying Malpractice Insurance

The Executive Committee recommends that this report be accepted as one of information.

Committee on Physical Medicine

The Executive Committee recommends that this report be accepted as informational.

Committee to Study the Income Level for Blue Shield

The Executive Committee was much confused by this report. It recommends that the Council refer it back to the committee for elucidation.

Committee to Meet with General Hawley

This report is informational only, and the Executive Committee recommends its acceptance as such.

MICHAEL A. TIGHE, Secretary

APPENDIX NO 3

REPORT OF THE COMMITTEE ON PUBLICATIONS

The *New England Journal of Medicine* has operated successfully so far this year. The outlook for next year is also bright. We hope that it will not be necessary to call upon the Society for any funds for the year 1947, but the situation is so uncertain, owing to the rise in price of materials, that we ask for an appropriation of \$5,000 to be drawn on if necessary. The estimated revenue and expenses for the year 1947 are shown on the statement which has been submitted to the Treasurer and the Committee on Finance. This statement is included in the report of the Treasurer. A full report of the operation of the *Journal* will be submitted at the annual meeting of the Council in May.

It has been customary to publish a *Directory of Fellows* every two years. The last one was published in 1945. Therefore a new directory should be published in 1947. The committee believes that it is important to publish a directory in 1947 because there have been so many changes in the addresses of fellows since the publication of the last directory. We therefore request an appropriation of \$2,000 for the publication of the Directory.

For the past year, the Committee on Publications has seriously considered the adoption of some sort of retirement plan for the full-time employees of the *Journal*. Since the employees of a non-profit educational organization are not entitled to the benefits of the Social Security Act, it seems

shall remain in the hands of the physician and not be shared with the school nurse

The Executive Committee recommends that the Council approve the recommendation providing that the Council authorize the President to appoint a subcommittee of three to act as liaison between the Society and the Massachusetts State Department of Mental Health

The Executive Committee approves the first part of the report dealing with Dr. Getting's program but notes that the last part concerns public-health personnel. If this were approved by the Council, it would commit the Society in a manner in which it should not be committed. It therefore recommends that the Council take no action on these lines on the ground that action on this subject is beyond the scope of the Society.

The remainder of the report of the Committee on Public Health is informational, and the Executive Committee recommends its adoption as such.

Committee on Postwar Planning

The Executive Committee notes that the first part of this report is informational. It recommends adoption of this part of the report.

The Executive Committee notes several recommendations. This Committee is in accord with all these recommendations except that which would authorize the creation of a special committee of five members to be appointed by the President, subject to confirmation by the Council, to consider the advisability of setting up a board of trustees within the structure of the Massachusetts Medical Society.

The Executive Committee recommends that the Council disapprove of this recommendation. In the discussion attending this subject, it came out that the Executive Committee, consisting of one representative from each district in the Commonwealth, had been performing what might be regarded as the functions of a board of trustees, but that there was a feeling in the Committee on Postwar Planning that there was at times a lack of over-all policy due to the size of the Executive Committee and the shortness of time (three years) in which any single member might hold continuous office. On the other hand, it was emphasized in this discussion that there never had been any difficulty in getting the Executive Committee together even in emergency session and that a board of trustees might result in too centralized a government, which might affect unfavorably the democratic character of the Society and alienate the interests of the ordinary member. The wisdom of setting up a board of trustees, which in the ordinary course of events might be expected to take over the functions now being satisfactorily performed by the Executive Committee, was seriously questioned. It was pointed out that the recommendations did not actually propose that such a board of trustees be set up, but only that a committee be authorized to study this subject. It was also pointed out that a board of trustees might be needed to give direction to the efforts of the Director of Medical Information and Education. There were district societies that reported their councilors as unanimously opposed to the proposal.

It was noted that the final recommendation by the Committee on Postwar Planning was that it be discharged. The Executive Committee in recommending that the Council adopt this recommendation also recommended that this discharge carry with it the expression of the Council's gratitude for a job well done and that this expression of gratitude be in a special manner directed toward the chairman, Dr. Root, who had given so generously of his time and talent over a period of years.

Committee Appointed to Nominate a Director of Medical Information and Education

The Executive Committee recommends the adoption of the recommendations contained in this report.

Committee on Postgraduate Assembly

The Executive Committee notes that this report contains two recommendations that a committee be appointed to arrange an assembly in 1947 and that the Council approve of the setting up of an independent organization to be known as the New England Postgraduate Assembly.

The thinking in the Executive Committee with regard to the second recommendation was that if the postgraduate

assemblies were to be operated by all the New England state medical societies, it was desirable that they be given sponsorship and direction by an organization that was a ready officially representative of these state societies. It was pointed out that the Council of the New England State Medical Societies was so representative and that at a meeting of the Council, which was scheduled for January 1, 1947, the taking over of this activity was to be considered by this council. It was explained that this council was made up of three representatives from each of the New England state medical societies and that it had its support from an equal assessment on each society and that that sum up in this time was one hundred dollars yearly. It was also pointed out that the manner in which the last assembly was operated demonstrated that this activity might be run at a profit.

The Executive Committee took no action on these two recommendations. The Secretary was instructed to ascertain the desires of the Council of the New England State Medical Societies in this matter and to make known in the report to the Council of the Massachusetts Medical Society what those desires were. The Secretary, as a representative of the Massachusetts Medical Society, was present at the meeting of the Council of the New England State Medical Societies, which was held in Boston on January 15, 1947. The following motion was adopted at that meeting:

That the Council of the New England State Medical Societies postpone action for the present relative to sponsoring the New England Postgraduate Assembly until it can obtain the point of view of the individual state medical societies regarding their participation as co-sponsors.

It was pointed out that the action called for by this meeting could not be consummated by many of the state societies before June, 1947, and that even if it was favorable to the proposition, this would be too late to begin to plan for an assembly to be held in the fall of 1947.

It seemed to be the feeling generally that an assembly should be conducted in 1947 on much the same basis as it has been in the past and that before it was time to plan for the 1948 assembly, the Council of the New England State Medical Societies would know whether or not this was an activity which it would take over. (The Secretary would like to say that all this indicates that the Council might see fit to approve the first recommendation of the Committee on Postgraduate Assembly and lay the second one on the table. It must be emphasized that the above is a suggestion which comes from the Secretary alone, the Executive Committee as a whole having had no opportunity to review the information here recorded.)

Committee to Study an Increase in Assessment of Dues

This report reviews the present activities of the Society and such other activities as have from time to time been discussed as properly belonging in its sphere. The discussion concerns itself with the costs involved and concludes that the dues will have to be raised if the program outlined is to be realized. It notes that at one time an increase of \$10.00 was discussed in the Executive Committee, which would make the dues \$20.00. While noting the needs of the Boston Medical Library and the necessity of helping to meet those needs, the report makes no specific recommendation as to the amount that the Society should contribute. The report concludes as follows:

After reviewing the suggestions for future plans for the Society, it may be necessary to raise the dues to \$20.00. With such a program as outlined above it will probably be necessary to make further study in order to present a comprehensive plan covering all contingencies for the present and the future. The dues should be raised sufficiently so that it will not be necessary to raise them again.

The following quotation from the report of the Committee on Finance was then read into the record:

In the future, the salary of the Director of Medical Information and Education will add a sum to our annual budget which can hardly be expected to be covered by our present sources of income. The appointment of such a director will call for an increase in dues or for some other method of raising the amount of his salary and the expenses of his office.

Executive Committee

Clerical	\$92 90
Meals	154 34
	<hr/>
Estimate November-December	\$246 24
	59 35
	<hr/>
	\$285 59

Legislative Committee

Printing	\$6 50
Postage	11 84
Clerical	67 75
Telegrams	140 98
Mailing	25 24
Reporting	146 48
Meals	221 84
Mr. Charles Dunn	3 075 00
	<hr/>
Estimate for November-December	\$3,773 63
	978 66
	<hr/>
	\$4 152 29

Public Relations Committee

Printing	161 75
Travel	24 00
Meals	249 50
Clerical	106 80
	<hr/>
Estimate for November-December	\$541 94
	107 85
	<hr/>
	\$649 79

Committee on Arrangements

Printing	\$624 25
Envelopes	44 94
Clerical	193 39
Publicity	10 25
Meals	2 76
Annual Meeting	8 470 66
Rebate on booth and tickets	72 25
	<hr/>
Estimate for November-December	\$9 418 50
	101 72
	<hr/>
	\$9,520 22
	14,781 19
	<hr/>
	\$5,260 97

Income

Estimated Profit

Committee on Ethics and Discipline

Meals	22 23
Clerical	115 78
	<hr/>
Estimate for November-December	\$138 01
	24 91
	<hr/>
	\$162 92

Finance Committee

Estimate for November-December

Committee on Medical Defense

Palmer Dodge	708 80
Estimate for November-December	189 89
	<hr/>
	\$898 69

Committee on Membership

Clerical	71 18
Meals	52 39
	<hr/>
Estimate for November-December	\$123 57
	54 53
	<hr/>
	\$178 10

Society Headquarters Committee

Supplies	309 55
Electricity	169 82
Cleaning	187 70
Rent	2 437 49
	<hr/>
Estimate for November-December	\$3 104 56
	959 89
	<hr/>
	\$4 064 45

Committee on Publications

Clerical

Committee on Public Health

Over Massachusetts Central Health Council	10 00
Meals	35 25
Clerical	5 67
	<hr/>
Estimate for November-December	\$50 92
	13 12
	<hr/>
	\$64 04

Committee on Industrial Health

Meals	79 91
Estimate for November-December	40 81
	<hr/>
	\$120 74

Committee on Tax-Supported Medical Care

Clerical	2 08
Meals	20 45
	<hr/>
Estimate for November-December	\$22 53
	14 38
	<hr/>
	\$36 91

Committee to Meet with Massachusetts Hospital Association

Clerical	66
	<hr/>
Military Postgraduate Committee	
Clerical	0 52
	<hr/>
Postwar Loan Fund	
3 per cent on 17 \$500 loans	\$252 00
Clerical	4 41
Leral	25 00
	<hr/>
Estimate November-December	\$281 50
	50 00
	<hr/>
	\$331 50

Postwar Planning Committee

Postwar Planning	
Meals	\$216 54
Clerical	214 54
	<hr/>
	\$431 08
	431 08
	<hr/>
Clinical Information Bureau	
Wages	1 676 47
Printing	27 4
Clerical	40 44
Telephone	157 34
Supplies	107 00
Postage	281 70
	<hr/>
	\$2,538 38
	253 5
	<hr/>
	\$2,791 86

Postgraduate Medical Education

Printing	\$612 70
Meals	281 59
Supplies	151 06
Mailing	20 00
Sanders Theater	544 97
Caterer	556 00
Lecturers	1 291 95
	<hr/>
	\$3 257 65
	257 6
	<hr/>
	\$3,515 25

Medical Economics

Printing	2 50
Meals	41 40
	<hr/>
	\$7 90
	7 90
	<hr/>
	\$15 80

Veterans Affairs

Printing	11 00
Meals	0 10
	<hr/>
	\$11 10
	61 10
	<hr/>
	\$72 20

Estimate for November-December

Committee on Fee Schedule

Meals	8 44
Printing	199 92
	<hr/>
	\$208 36
	75 00
	<hr/>
	\$283 36

Estimate for November-December

Committee to Study Malpractice Insurance

Estimate for November-December	400 00
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"Committee of 7"

Meals	14 5
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APPENDIX NO 5

BUDGET FOR 1947

Expenditures 1946	Salaries	Budget 1947
\$3 500 00	Secretary	\$4 000
4 400 00	Executive Secretary	4 800
2 250 00	Treasurer	2,500
	Expenses of Officers etc	
170 00	President	500
0 00	President Elect	1,000
5 679 68	Secretary	2,000
2 400 55	Treasurer	1,000
5 040 99	Delegates to A M A	200
200 00	Shattuck Lecture	600
543 20	Cotting Luncheons	
4 247 90	General administrative expense (under supervision of President and Secretary)	10,200*
	Committees Elected by District Societies	
285 59	Executive	400
4 152 29	Legislative	5 000
649 79	Public Relations	600
	Standing Committees	
(profit)	Arrangements	200
162 92	Ethics and Discipline	50
20 25	Finance	25
898 69	Medical Defense	1,500
178 10	Membership	100
4 064 45	Society Headquarters	7 500†
3 12	Publications	7 000‡

*Include salaries of new clerical assistants (Miss Kelley, \$1 872 Miss Biggy \$1 820 and Miss Cowles \$2,405)

†Includes cost of new Addressograph (\$2 100) Multigraph (\$550) four typewriters (\$595) and supplies

‡Includes \$2 000 requested for publication of 1947 Directory

only reasonable that some provision should be made for retirement allowances, when these people reach a certain age. Indeed, many commercial companies have, in recent years, adopted retirement plans that supplement the Social Security benefits.

At the last meeting of the committee, held on December 4, it was suggested that, since the Society has an appreciable number of full time employees, it likewise might consider a retirement plan, and that if such a plan were adopted, it would be well for the *Journal* to follow an identical plan.

The committee therefore makes the following recommendations to the Council:

That the advisability of adopting some sort of retirement plan for the full-time employees of the Society be referred to a committee of the Society, either an existing committee or a specially appointed committee according to the desires of the President, and that, if the adoption of such a scheme seems desirable, a specific retirement plan be presented to the Council, subject to approval by the Committee on Finance, if the matter was not referred to said committee.

Dr William Dock, Director of Medicine, Long Island College of Medicine, Brooklyn, New York, has been secured to deliver the Shattuck Lecture in 1947.

APPENDIX NO 4

REPORT OF THE COMMITTEE ON FINANCE

The figures which make up the bulk of the report of the Committee on Finance are not to be regarded as a complete accounting of the finances of the Society. They represent a reasonably accurate estimate of expenditures based on the amounts paid out by the Treasurer during the first ten months of the current year plus an additional 20 per cent intended to cover the probable expenses for the remaining two months. This estimate, together with requests received from the various committee chairmen, serves as the basis of the budget which the by-laws of the Society require us to recommend to the Council for the proximate fiscal year. For purposes of comparison, similar items of expenditure for the current year are recorded, together with the estimates which made up the 1946 budget. We have appended similar estimates of income received by the Society during 1946.

A comparison of expenditures with income shows that we are operating well within our resources. Expenses were less than the amount anticipated in the 1946 budget, and income was greater, for example, income from dues amounted to approximately \$52,000 instead of the expected \$45,000. In the future, the salary of the Director of Information and Education will add a sum to our annual budget which can hardly be expected to be covered by our present sources of income. The appointment of such a director will call for an increase in dues or some other method of raising the amount of his salary and the expenses of his office.

Most of the items in the budget are self-explanatory. Unusually large items are explained in the footnotes. The amounts requested by the committee chairmen have in most instances been reduced to a slight degree. This reduction is based on the fact that items referring to clerical services were subtracted in accordance with the expressed offer of the secretary, Dr Tighe, to provide facilities at the Society headquarters for the performance of all the clerical work of the various committees so far as possible. It is hoped that this will relieve the committee chairmen of much clerical work. The plan is intended to assist them, not of course to interfere with their present methods except in so far as it will work for greater convenience and efficiency. The budget for headquarters committee expense and general administrative expense reflects this plan, as supplies and all salaries for clerical assistants are included in these items.

FRANCIS C HALL
FABYAN PACKARD
BANCROFT C WHEELER
CHARLES F WILINSKY
ROBERT W BUCK, *Chairman*

DETAILED EXPENDITURES — 1946

New England Postgraduate Assembly

Printing	\$533.84
Meals	157.60
Advertising	115.00
Clerical	37.21
Mailing	239.83
Supplies	108.30
Telephone	8.95
Postage	15.00
Cash for meeting	100.00
Refund tickets and a bouncing check	31.25
Speakers	4,619.96

Total expense \$5,964.97

Income \$6,802.45
Profit 837.48

Refunds to District Medical Societies

Refunds \$4,000.00

Council of the New England State Medical Societies

Contribution 100.00

Massachusetts Medical Clerical

Miss Kelley since July 1 \$40.00
Miss Biggy since September 1 280.00

\$420.00

\$85.00

\$1,405.00

Estimate November December

Salaries 1946

Secretary \$3,500.00
Executive Secretary 4,400.00
Treasurer 2,250.00

Expenses of Officers and Committees

President's Expense

Newslip 10.00
Clerical 75.04
Meals 9.61
Travel 45.00

\$139.65

30.35

\$170.00

Secretary's Expense

Printing \$901.57
Clerical 1,522.98
Supplies 140.25
Reporting 208.50
Postage 251.78
Mailing 60.43

\$3,091.51

588.11

\$3,679.68

Estimate November December

Treasurer's Expense

Miscellaneous \$37.50
Premium on bond 315.00
Auditors 18.00
Rent box \$370.50

370.50

446.14

1,164.51

10.14

163.80

\$2,155.09

245.46

\$2,400.55

Delegates to A M A Expenses

Expenses 2,252.97

Estimate for November December 788.02

(December meeting) \$3,040.99

Shattuck Lecture

Expense 200.00

Cotting Luncheons

Expense 543.20

General Administrative Expense

Travel 912.75
Clerical 145.32
Printing 911.79
Telephone 484.30
Meals 96.92
Supplies 311.74
Mailing 29.11
Postage 48.50
Premiums Blue Cross and Blue Shield 44.25
Miscellany (Journal account) 744.72
Newslip 15.00
Funeral flowers 15.00

\$3,760.00

487.90

\$4,247.90

Estimate for November December

It is recommended that legal counsel be asked to draw up a written agreement which would embody these general terms

APPENDIX NO 9

REPORT OF THE COMMITTEE TO STUDY INCREASE IN ASSESSMENT OF DUES

The committee held a formal meeting on Sunday, December 8, 1946, at 2.30 p.m. There were present Dr. Edwin Gardner, Marion, Dr. John W. McKeon, Worcester, Dr. Kenneth L. MacLachlan, Melrose, and Dr. Frank R. Ober, Boston. Dr. N. Newall Copeland, Pittsfield, was absent.

The members were written to on November 7, 1946, and advance information was sent each one relative to annual dues of all the New England state medical societies and the Massachusetts Dental Society, as well as the Treasurer's report at the last annual meeting. No reply was received from the absent member, although two letters were written to him.

In discussing the matter of increasing the annual assessment, your committee considered

- 1 The present cost of running the Society
- 2 The raising of salaries of the central office personnel
- 3 The raising of the salaries of the Treasurer, Executive Secretary, Secretary and Miss Gaston
- 4 The salary and expenses of the Director of Medical Information and Education
- 5 The possibility that the office of the Secretary of the Society be made full time and receiving adequate compensation therefor
- 6 The relation of the Boston Medical Library to the Massachusetts Medical Society
- 7 The advisability of some form of financial support to widows and orphans of physicians
- 8 The advisability of financial aid to certain physicians incapacitated by chronic illness or some other cause and unable to support themselves and their families
- 9 A retirement fund for the full-time workers of the Society
- 10 The fact that the present headquarters are totally inadequate for the transaction of the Society affairs. There is only one room for committee meetings
- 11 A long-range plan to establish a headquarters which will house the Society

These paragraphs are discussed in some detail as follows

1 Given a membership of 6000 and dues of \$10.00 per year, plus excellent general economy, the Society can manage but this does not allow for critical expansion which is needed right now. In bad times, there would not be enough without jeopardizing the general fund.

2 Salaries of the clerical force have been raised this year and the clerical force has been increased. The present cost per year is \$5,876, an increase of \$512.

3 The yearly compensation of the Treasurer is now \$2,500, of the Secretary, \$4,000, of the Executive Secretary, \$4,800, and of Miss Gaston, \$2,184—a total of \$13,484. The total increase of salaries is \$2,996.

4 It has been recommended by the Committee of Seven that a Director of Medical Information and Education be secured at a salary of \$7,500 for the first year, which is to be increased by \$500 each year until a maximum of \$10,000 is reached. In addition to this sum, there must be added an indefinite sum for necessary expenses. This position is to start July 1, 1947.

5 Your committee is of the opinion that the time has arrived when it is to the best interests of the Society to consider seriously the advisability of having a full-time secretary on a more permanent basis than exists now. An adequate salary must be provided to meet this situation. The duties of the Secretary's office are increasing steadily and some time in the not-too-distant future it will be a continuous performance. The office of a full-time secretary would be open all the time in order that physicians may be able to seek advice of the secretary any weekday. This would in itself make the Society more valuable to its members.

6 The relation of the Boston Medical Library to the Massachusetts Medical Society was considered at some length. The Boston Medical Library is in need of financial assistance. It is believed by your committee that the Library is a real asset to the Massachusetts Medical Society. If through lack of sufficient income, it became necessary for the Library to close its doors, the whole medical profession of the Commonwealth would suffer.

The trustees of the Library have tried to get needed help from many sources, but without success. This is the third largest and one of the oldest medical libraries in the United States. Its membership is small—nine hundred and thirty-two. Its dues are \$15.00 per year. It is used by a great many who pay nothing, and many of these will not become members because they get service free. This situation is unfair to the Library and those loyal members who do pay. The Library can be made useful to every member of the Society.

The *New England Journal of Medicine*, which is owned and run by the Massachusetts Medical Society, is a constant user of the facilities of the Library. This is an important factor in the publishing of the *Journal* because bibliographies of articles must be checked. The fact that the Library is in the same building as the *Journal* makes this easy and saves a great deal of expense and time. This would not be true if there were no Library available.

This is a distinct asset to the Society and is one of the many reasons why the *Journal* is having so much success and a constantly increasing distribution. It would seem, therefore, that the Library is a real asset to the Massachusetts Medical Society for which there does not seem to be an adequate return. It is recommended that the Society subsidize or otherwise help the Boston Medical Library so that this valuable institution will not go under.

7 The committee recommends that some form of financial support be made to needy widows and orphans of physicians.

8 It further recommends that a fund be set up to aid and assist those physicians who through no fault of their own find themselves incapacitated through illness, injury, or age, and are not able to support their families. The Massachusetts Benevolent Society has an income of \$5,000 a year and is at present helping seventeen people who fall into this category. This society would probably be willing to integrate their fund with any proposed plan of the Massachusetts Medical Society.

9 There should be also a retirement fund for the full-time members of the central administrative office of the Society.

10 The present office space is totally inadequate for the proper conduct of the business of the Society. There is only one room in the building available for committee meetings, therefore, many meetings are held outside the building and at some extra cost. It would be to the advantage of all concerned could they be held at the headquarters.

The Headquarters Committee voted that the Society secure more room from the Library by helping the Library to construct stacks for books and so forth that are stored on the floors and against the walls of the building, thus taking up space that would be freed could the Library afford to construct stacks and secure more help in placing and cataloging these books. This would give us more urgently needed rooms for meetings and business purposes and would be a distinct help for the present.

11 Your committee is in sympathy with the proposed plan of the Headquarters Committee of the Society. This proposed plan is a long-range one and depends largely on securing a site near the Library and the *Journal*. The Massachusetts Medical Society should have a home adequate to take care of all the facilities of the Society for at least fifty years. This means sufficient office and committee rooms, a larger banquet hall for the Council, a kitchen for the benefit of the working officers and clerical help at the headquarters. The possibility of an auditorium large enough to hold the annual meeting might well be considered. Smaller meeting rooms in the same building would be necessary.

With this long-range plan in mind, an increase in the annual assessment might be a good thing to do now, so that a portion of such increase could be set aside and allowed to accumulate as a sinking fund to be used in any new additions or construction of adequate facilities for the future.

The present dues are \$10.00 per annum, which includes the subscription to the *Journal* and the "turnback" to the dis-

APPENDIX NO 8

REPORT OF THE COMMITTEE APPOINTED TO NOMINATE A
DIRECTOR OF MEDICAL INFORMATION AND EDUCATION

Because of elapsed time since the Council assigned this study to the committee, it seems desirable to review the whole situation

The growth of the Society and expansion of activities have been such that it became increasingly apparent to several committees and individual fellows that the time had come to create a new position for the handling of public relations, legislation and other matters which would inevitably arise in future Society activities. Toward this end, a special committee, the Committee on Public Information, studied the situation last year, conferring with Society committees, public relations experts, health educators, newspaper and radio men and so forth and then, together with the Postwar Planning, Legislative and Public Relations committees, placed the matter before the Council. On October 3, 1945, the following resolution was adopted by the Council

WHEREAS, We consider that the Massachusetts Medical Society is under obligation to make its educational facilities of increasing usefulness to fellows, to all licensed physicians in Massachusetts and to the public, therefore, be it

RESOLVED, That the Massachusetts Medical Society hereby creates a new position, its holder to be known as the Director of Medical Information and Education, charged with the duty of promoting in an ethical manner the educational usefulness of the Society to its fellows and to the public and also charged with the performance of such other duties as the Society or the Council may require, and be it further

RESOLVED, That such a Director of Medical Information and Education shall be appointed by the Council on proposal of a Committee of Seven named by the President

The President appointed this committee as follows: Elmer S. Bagnall, David Cheever, Roger I. Lee, Charles E. Mongan, Frank R. Ober, Walter G. Phippen and George L. Schadt, with the President and President-Elect members *ex officio*.

Since retiring from the presidency of the Society in May, 1946, Dr. Reginald Fitz has been a party to the committee's discussions, as has President-Elect Edward P. Bagg.

The first meeting of this committee was held on October 24, 1945. Dr. Fitz was appointed as the first chairman and Dr. Bagnall was elected secretary.

Since that time, numerous meetings have been held. The committee felt that the selection of the right man required a definition of his duties far more precise than is given in the vote of the Council, to the end that his qualifications and attainments should be adapted to those duties. Therefore, they first studied the broader aspects of this field. Letters were sent to all state societies. Replies were received from more than half, some of which sent voluminous evidence of activities. Many issues and problems were brought to light. Letters to Dr. Creighton Barker, who holds a similar position in the Connecticut State Medical Society; Dr. Olin West, secretary of the American Medical Association; Thomas A. Hendricks, secretary, and Dr. Joseph S. Lawrence, director of the Council on Medical Service and Public Relations of the American Medical Association brought forth advice and recommendations. The presidents of our district societies were contacted by letter for assistance in locating a man but only one or two suggestions were forthcoming.

In May, 1946, the committee made a report to the Council which said, in part

The committee feels that much of the work of the new director must at first be of an exploratory and tentative character and that its final emphasis and value cannot be predicted. Much will depend on the particular talents which he may bring to his office. They believe that ideally the incumbent should be a physician, a member of the Society, experienced in practice, and in early middle life, so that before him may stretch a long career of usefulness, which will steadily increase with his experience. Such a man must, of course, be on a full-time basis, and receive a salary sufficient to enable him to relinquish the income from a successful practice. His appointment should be terminated on his reaching a prescribed age, as in the case of academic or teaching appointments.

The committee has failed thus far to discover a suitable candidate with all these qualifications. They agree that the selection of the candidate is a matter of paramount importance and have preferred to proceed with caution rather than run the risk through haste of committing a grave error. This report, therefore, is one of progress and contains no recommendation.

Although several men had been suggested as possibilities for the position of Director of Medical Information and Education, none were considered by the committee as having the proper qualifications until the name of Dr. John F. Conlin was brought to the attention of the committee by letters from Dr. Elliott Cutler, Dr. John Fallon and Dr. Sidney Farber.

Investigation brought out these essential facts about Dr. Conlin:

John Francis Conlin was born in Schenectady, New York, in 1908. His father was a research metallurgist with the General Electric Company. He was educated in the public schools of Schenectady and attended the Holy Cross Preparatory School from 1923 to 1926.

From 1926 to 1932 he was under monastic orders in the Passionist Monasteries at Dunkirk, Springfield, Scranton, Baltimore and Boston. In 1932, he decided that he was more fitted for the study of medicine than for a career in the Church.

He, therefore, returned to the secular life, attended Boston College from 1932 to 1934, receiving the degree of Bachelor of Science, and attended Tufts College Medical School from 1934 to 1938. He was president of his class throughout the four years of medical school and was chairman of the Student Activity Board during his senior year. On graduation, he received the "Alumni Award" of the medical school.

He served an internship in 1939 and 1940 at St. Elizabeth's Hospital in Brighton and served as resident at the John Adams Hospital in Chelsea from 1940 to 1941. He entered active duty with the Army in 1942, he went overseas in 1944, he returned a lieutenant colonel in 1945 and was discharged with a full colonel's rating in 1946.

During the 1945-1946 season, he came to the attention of several committees in the Society because of his assignment to fight the Antivivisection Bill before the Legislature last year. During part of this period he worked with the Veterans Administration and in the fall of 1946 he entered the Harvard School of Public Health.

He joined the Massachusetts Medical Society in 1941 and he was elected a Councilor in 1946. He was appointed to the Committee on Arrangements last spring in recognition of the splendid job he had been doing on the antivivisection legislation.

At the meeting of the committee on September 20, it was decided to interview Dr. Conlin either individually or in groups.

A meeting was held on November 14. At that time Dr. Conlin had been interviewed by all members and had made a most favorable impression on the majority of the committee. Discussion ensued as to his qualifications, his duties, salary and so forth. It was voted that the President and President-Elect, as a subcommittee, interview Dr. Conlin regarding salary, not to exceed \$10,000, and that if satisfactory financial arrangements developed, he be nominated for the position of Director of Medical Information and Education.

From the report of this subcommittee, the Committee of Seven makes the following recommendation to the Council:

The Committee of Seven proposes that Dr. John Francis Conlin be appointed by the Council as Director of Medical Information and Education.

Dr. Conlin will be available at the close of the school year, and it is recommended that he begin as of July 1, 1947, at the salary of \$7,500 per annum, plus ordinary traveling expenses, and with appropriate vacation periods. If his services are satisfactory and if he is satisfied with the work as it develops, he is to receive an increase of \$500 on January 1, 1948, and on each January 1 thereafter until the maximum salary of \$10,000 would be reached on January 1, 1952. If there should be gross inflation in our national economy, adjustments should be expected. There should also be an understanding concerning a mutual termination of the agreement.

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CASE 33161

PRESENTATION OF CASE

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The temperature was 98.6°F, the pulse 104, and the respirations 20. The blood pressure was 154 systolic, 94 diastolic.

Examination of the blood revealed a hemoglobin of 16 gm and a white-cell count of 13,400, with 79 per cent neutrophils. X-ray examination showed a soft-tissue mass about the right lower fibula into which irregular spicules of bone extended from the fibula. The margins of the bone were slightly irregular and indefinite, and there was a suggestion of periosteal-layer formation. The medullary structure was disorganized, and the cortex had a somewhat moth-eaten appearance. Examination of the chest was negative.

Operation was performed on the second hospital day.

DIFFERENTIAL DIAGNOSIS

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strict societies. A questionnaire on dues was sent to the New England state medical societies, as it was thought that information on this subject would be valuable to us all. The following information was obtained:

New Hampshire Medical Society	\$10
Maine Medical Association	35
Rhode Island Medical Society	40 (\$25 first year of practice)
Connecticut State Medical Society	20
Vermont State Medical Society	35 (of this, \$5 is earmarked for needy physicians)

In summary, it appears that an increase in dues will be needed for the following reasons:

- 1 To meet our old obligations and our new obligations
- 2 To provide a fund or funds for retirement purposes as recommended
- 3 To help the Boston Medical Library and increase the room of the present headquarters
- 4 To develop a building fund
- 5 To provide a sinking fund in order to take care of needy physicians

The committee has recommended that the annual dues be raised to \$20.00. After reviewing the suggestion for future plans for the Society, it may be necessary to raise the dues to \$25.00. With such a program as above outlined, it will probably be necessary to make further study in order to present a comprehensive plan covering all contingencies for the present and the future. The dues should be raised sufficiently so that it will not be necessary to raise them again.

APPENDIX NO 10

REPORT ON THE TRANSACTIONS OF THE HOUSE OF DELEGATES OF THE AMERICAN MEDICAL ASSOCIATION

The following is a report of the supplementary meeting of the House of Delegates of the American Medical Association at Chicago December 7, 8 and 9. This is the first such meeting ever held not of an emergency character. Its purpose is to lighten the amount of work to be done at the annual meeting.

There was a full attendance of delegates. An interesting international note was the dropping of the representation from the Philippine Islands. These islands now constitute an independent state. At this meeting there were no addresses by the various officers, and the House proceeded at once to the matters at hand (and there were many). It was stated that the membership had increased by 3374, the total now being 129,145. Reference committees were immediately appointed by the Speaker, and as usual their work was long and exacting in most cases.

On the morning of the first day, there were given to each member copies of the so-called "Rich Report" and of the report of the Interim Committee, this committee having been appointed to analyze and make recommendations as to acceptance or rejection of many recommendations in the Rich Report. It might be of interest to know something of this whole affair.

Early in 1946, the trustees of the American Medical Association employed the Rich Associates (investigators of non-profit organizations only) to make a survey of the entire organization of the American Medical Association, with recommendations for its greater usefulness, especially along the lines of public relations. About five months were spent on this survey. It was briefly alluded to by Dr. Sensenich, president of the Board of Trustees, on the last afternoon of the annual meeting of the House of Delegates in San Francisco. He stated that the report had just lately been received, and that the House of Delegates was merely being informed briefly as to what in general it contained. This was not too satisfactory an arrangement or disclosure, and left the members in a state of critical curiosity as to just what this Rich Report contained. One may say that this statement by Dr. Sensenich was not too well timed. To offset this, the Speaker of the House later made the Committee on Executive Sessions, which had completed its work

in San Francisco, an interim committee. This committee consisted of Bates, of Pennsylvania, Carey of Texas (who never came to any of the meetings), McGlendon, of California, Lewis, of New Jersey, Hein, of Ohio, Bunce, of Georgia, and Scannell, of Massachusetts. This committee met with the trustees at Chicago in September, 1946, again met as a committee alone on December 7 in Chicago, and with the Board of Trustees on Sunday, December 8. The committee's report was then prepared and delivered to the House of Delegates on Monday morning. It was felt that this report of ours might be the high spot of the transactions of the House of Delegates and that is just what it proved to be. The House of Delegates went into Executive Session on Tuesday morning and discussed paragraph by paragraph both the Rich Report and the report of the Interim Committee. This consumed a good portion of Tuesday. We had felt that the portion of our report having to do with relations of the National Physicians Committee and the American Medical Association might prove most controversial, and that actually was the case. We recommended that this relation be studied further, and this was agreed on. The same committee, after giving the matter continued study, is to report to the House of Delegates in Atlantic City in June, 1947. Incidentally, the Rich Associates have been hired as continuing counsel to do the work suggested in their report (except as modified by the House of Delegates) for one year. Many of their recommendations were excellent, others were not so acceptable. The latter were rejected. Matters pertaining to public relations and publicity emanating from the Rich Associates are to be cleared through the office of the General Manager. The recommendations of the Committee were well received and practically universally accepted, and did much, we feel sure, to facilitate progress and to evaluate the report and its recommendations. It would take much too long to enumerate all the recommendations in this report, but the keynote of them all is to separate distinctly the functions of scientific interpretation, medical economics, socialized medicine, and the direction of public relations. They may be summarized as follows:

Vitalization of Hygeia for the reading public

Bureau of Medical Economics. In this connection, there has been appointed a Mr. Dickinson as Director of Economic Research (an admirable selection).

Public Relations. More positive type of program required, more publicity for the reading public, always, however, to be cleared through the office of the General Manager.

Health Education. An instrument of great potential importance in public relations, not yet exploited to the full, with radio, various publications, releases and so forth. This whole subject to be greatly expanded with closer liaison between state and county societies and volunteer service plans.

Council of Medical Service. Expansion of these activities with conferences on invitation from constituents or component societies at local levels.

News Letter. To be further improved and given wider dissemination.

Council of Industrial Health. More attention to be paid to industrial and consumer groups, in view of recent developments in connection with the United Mineworkers' Health Fund and similar labor, management and consumer groups.

Radio. Employment of junior radio specialist, backed by highly experienced professional counsel, if, after study, it is justified by need and cost (an expensive item).

Speakers' Bureau. This should be utilized to its fullest capacity and should be implemented by conferences with state organizations.

Prepayment Medical Care. At the present time, there are five million members enrolled and all the states but two have plans in operation.

The Women's Auxiliary. The recommendation that this be developed in states where it is not now in operation.

It must not be thought that this consideration of the Rich Report was the only subject on the agenda, but to state them all would be unprofitable. The minutes of this supplementary meeting will not be printed in the *Journal of the American Medical Association* until sometime in January,

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fibula The lower two thirds of the fibula shows a destructive process involving both the cortex and the medullary structure The periosteum of the lower end of the fibula is raised and has formed new bone For most of its length, the tumor mass is entered by narrow, irregular, calcified spicules

osteomyelitis was made, after the arm had been amputated I consider it important in doing a frozen section that the surgeon assume the responsibility of the diagnosis, share the responsibility of the gross diagnosis with the pathologist and bear with him in his difficulty in making a diagnosis on

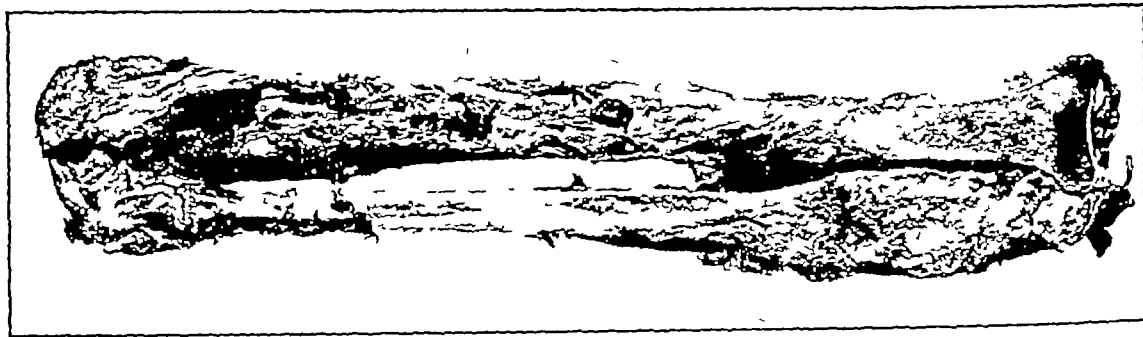


FIGURE 1 Photograph of Fibula and Tibia

At the right may be seen the sectioned tumor in the lower end of the fibula, as well as the sectioned normal tibia

projected at right angles from the shaft of the fibula The tibia is not involved

DR DALAND Are we dealing with infection or with tumor? If a tumor, was it malignant or benign? I do not believe that we have enough evidence to make a diagnosis of infection The x-ray films do not suggest osteomyelitis to me The temperature and the systemic findings are not severe enough for osteomyelitis I do not know how long the penicillin was continued or how complete the therapy was We are told that the patient did not receive any benefit from it, but we should not expect him to unless the drug was given in large amounts for a considerable time

I think that this case comes down to a diagnosis of Ewing tumor or osteogenic sarcoma — the raised periosteum is always suggestive of the former, and the destruction of the cortex can be due to either one or the other The soft-tissue mass is not easily seen in the film but does not seem nearly so impressive as one would expect with a mass 15 cm in diameter There is not so much new-bone formation in the mass as I should expect in an osteogenic sarcoma I am inclined to think that this was a Ewing tumor

This is a difficult diagnosis to make on frozen section, as has been said before If I were going to treat this patient I should do a biopsy and wait until the pathologist had got his final sections through before going ahead with amputation I recall a case like this in a man on whom a diagnosis of Ewing tumor was made preoperatively by the radiologist, by the surgeon who operated and by the pathologist on frozen section A few days later the decision was changed, and the diagnosis of chronic

frozen section I prefer to wait and do a radical operation after all the opinions are in

I believe that the diagnosis in this case is a Ewing sarcoma

DR MALLORY Dr Taylor, you saw this patient have you any comments?

DR GRANTLEY W TAYLOR I went through the same process of reasoning as Dr Daland did We find constantly in bone tumors that we cannot make a diagnosis by palpation I sympathize therefore when the pathologist has to make it histologically, but it seemed obvious that the patient in the case under discussion had a malignant tumor of the leg, and the differential diagnosis rested between an osteogenic sarcoma and a Ewing tumor We included both in our preoperative diagnosis believing that the pathologist could make the decision on frozen section or could at least decide that it must be one or the other and rule out benign conditions I am interested in Dr Daland's anecdote in which amputation was carried out for osteomyelitis, because I had supposed that an adequate frozen section would reveal whether one was dealing with a neoplasm or an inflammatory condition

CLINICAL DIAGNOSIS

Osteogenic sarcoma of fibula?
Ewing tumor of fibula?

DR DALAND'S DIAGNOSIS

Ewing sarcoma

ANATOMICAL DIAGNOSIS

Ewing tumor of fibula

PATHOLOGICAL DISCUSSION

DR. MALLORY One of the real problems when a frozen section is done on a bone lesion is that the specimen is likely to contain spicules of calcified material that prevent an adequate section. A frozen section was done during operation on this patient, and the pathologist was certain that the tumor was malignant but uncertain regarding the type, although he favored osteogenic sarcoma because a considerable amount of new-bone formation was recognized. When the final sections came through, however, it was quite obvious that the bone formation was in the stroma and periosteal remnants. No bone was being formed by tumor cells. The latter were of the type characteristic of Ewing tumor, which was the final diagnosis of this case. The tumor had destroyed the lower third of the fibula and had elevated the periosteum as far up as the midpoint of the shaft (Fig 1).

CASE 33162

PRESENTATION OF CASE

A twenty-nine-year-old Italian housewife entered the hospital because of lower abdominal pain, chills and fever.

Four years before entry the patient had had a bout of crampy pain in the right lower quadrant of four months' duration. This was treated conservatively until she had a sudden increase in severity of the pain associated with vomiting, chills, fever and the passage of clots and brownish liquid by vagina, laparotomy was then performed at another hospital. The appendix was found to be retrocecal and held down by a few adhesions but was otherwise normal. The right fallopian tube and right ovary formed an adherent inflamed mass low in the pelvis. When this mass was freed, a few drops of thick pus escaped, this was removed with suction. The markedly swollen and injected right tube was removed. The left tube and ovary were normal. There was drainage from the abdominal wound for five months, but the symptoms were completely relieved. Eighteen months before entry the patient had been delivered of a normal full-term infant. The post-partum course was uneventful. For six months before entry she had had a profuse, malodorous leukorrhea requiring daily douches. Six weeks before entry the last normal menstrual period had occurred. Three weeks before entry she was in a minor automobile accident in which the left lower abdomen was struck against the steering wheel. She suffered no great discomfort from this but noted a slight amount of vaginal bleeding that night and the following day. Six days before entry the patient again had some slight spotting. On the following day, while doing her housework, she was suddenly seized by a violent gniping pain in the left lower quadrant that was severe enough to cause her to lie down,

to "thrash about" and to vomit repeatedly. At the same time she began to pass brownish fluid and blood clots by vagina. After one or two hours of vomiting she fainted, collapsing on the floor. She regained consciousness after a few minutes. A physician was called, and the pain was somewhat relieved by a hypodermic injection, it gradually became less crampy and more general, involving both flanks and the entire lower abdomen. Vomiting and retching persisted, although no food was taken. The patient also continued to have scanty vaginal bleeding. On the day before entry she began to have shaking chills, and temperature rising to 101°F. She had had no pain or burning on urination, frequency or nocturia. The bowels had been regular except for obstipation since the start of the acute episode.

She had begun to menstruate at the age of twelve years, and the periods had always been rather irregular, occurring at an interval of twenty-five to thirty-one days and lasting about three days. She had never lactated properly and had not nursed her last child.

Physical examination revealed a slightly built, poorly nourished woman lying in bed restlessly and complaining of headache and occasional sharp pains in the left lower quadrant. She was somewhat disoriented regarding time. The skin was dry and cool. The lungs were clear. There was moderate diffuse abdominal tenderness most marked in the left lower quadrant, where a vague mass could be felt. The posterior fornix of the vagina was full of dark-brown, liquid blood. The cervix was firm. The uterus was normal in size.

The temperature was 101°F, the pulse 90, and the respirations 20. The blood pressure was 110 systolic, 20 diastolic.

Examination of the blood showed a hemoglobin of 11.0 gm and a white-cell count of 22,200. The urine was normal. The vaginal discharge was negative for beta-hemolytic streptococci and gonococci by smear and culture.

Under penicillin therapy the temperature dropped to normal in three days. On the third hospital day she had another episode of vaginal bleeding, passing clots for an hour and continuing to spot slightly. On the fifth hospital day she was completely free of abdominal complaints. The white-cell count had dropped to 18,800. Two days later, the mass in the left vault was found to be considerably decreased in size, moderately movable and no longer confluent with the uterus.

On the tenth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. FRED A. SIMMONS I am unable to understand, how, with the condition of the patient on admission to the hospital, an operation could have been postponed until the tenth hospital day. The

surgeon had a great deal of courage to wait that long

The history revealed a proved diagnosis of pelvic inflammation, with pus exuding from one tube, three years before the present admission. In spite of that proved pelvic inflammation or salpingitis, a normal full-term pregnancy had occurred eighteen months previously, and the menstrual period was two weeks overdue on admission, although she had been having irregular, spotty vaginal bleeding during the interval.

Five days before entry the patient had an intraperitoneal accident of some kind that was severe enough to cause vomiting, severe pain and unconsciousness. Someone had the temerity to administer a hypodermic injection without operating on her. On the day before admission she had chills and a temperature of 104°F, associated with continuing abdominal pain. On admission a mass was palpated. I am emphasizing these points— inflammatory disease, delayed menstrual period, abnormal metrorrhagia, elevated white-cell count and a mass palpable on abdominal and pelvic examination—because by definition alone it is impossible to rule out an ectopic pregnancy. I believe that it is the policy of the gynecologic service to consider such a condition ectopic pregnancy, and operation was indicated at that time. A possible reason for the delay in operation was that the diagnosis lay between ectopic pregnancy, pelvic inflammation, twisted ovarian cyst and some other pelvic infection, such as tuberculosis, and that the results of the Aschheim-Zondek test were awaited. According to the history the Aschheim-Zondek test could have been negative or positive—negative if there was no viable placental tissue but positive if viable products of conception were still present.

In 1945 at one of these conferences, I discussed the case* of a woman in her thirties with a history of metrorrhagia associated with pelvic findings similar to those in the case under discussion. I failed to make the correct diagnosis, which was tuberculosis of the tubes, because it had not been my experience to find abnormal menstrual bleeding with tuberculosis of the pelvic viscera. The usual history is one of amenorrhea. At any rate, tuberculosis must be considered in this patient because she was described as being poorly nourished and because she had a pelvic infection. About four years ago there was a patient on the wards with a finally proved diagnosis of actinomycosis of the tubes who had some of the same findings—namely, drainage from an abdominal wound for weeks or months following a pelvic operation and a mass, with cachexia, fever and high white-cell count. About thirteen years ago, in the Emergency Ward, a patient was admitted who had had a two-month

history of abdominal pain, flowing and a mass, and for some reason or other no one mentioned ectopic pregnancy. At operation 200 cc of old blood was found in the peritoneal cavity, and the diagnosis of ectopic pregnancy was unmistakable.

The record does not state whether the appendix of the patient under discussion had been removed at the initial operation. If not, one could not fail to consider appendicitis as a cause of the symptoms. The history indicates that the right ovary was not disturbed at the initial operation at which the right tube was removed. Therefore, if the patient had had tuberculosis of the right tube, the other tube or the ovaries, or both, may have been involved. The drainage from the abdominal wound points toward tuberculosis. I paid particular attention to the fact that there was sufficient insult to the peritoneal cavity five days before entry to cause vomiting and unconsciousness as evidence of an acute pelvic process of some kind, such as perforation of a pus-containing sac or a blood-containing sac.

After penicillin therapy, the temperature dropped to normal in three days. If a patient has acute pelvic inflammation and is given chemotherapy, the symptoms subside, the temperature becomes normal, the tenderness disappears and the patient appears well, although a smoldering infection may continue in the adnexa that may flare up weeks, months or years later.

I do not see how we can get away from the facts that the patient was flowing abnormally, that the menstrual period was overdue at the time of admission and that she had a mass. The size of the mass is not described in the record of the pelvic examination, but the statement is made that the mass had "considerably decreased in size" on the seventh day.

As often happens in these conferences the diagnosis entertained on the first reading of the record remains the last, and on the basis of the history and on the physical findings, I must make a diagnosis of ectopic pregnancy.

DR TRACY B MALLORY Dr Sturgis, will you give us your impression of the case?

DR SOMERS H STURGIS I might say that the clinical impression when the patient was first seen was a little more definite than the record indicates, in that the mass was definite, fairly large and fluctuant. On pelvic examination we considered it characteristic of a tubo-ovarian abscess. We were not so impressed as Dr Simmons has been by the overdue period and the bleeding, and I think that we may have missed something. At that time, with the history of inflammation in the past, the clinical appearance of the patient made us think that she had a tubo-ovarian abscess and we were interested to see how it would respond to penicillin. We were pleasantly surprised when the mass decreased in size and became more movable under that treatment.

*Case records of the Massachusetts General Hospital (Case 31152)
New Eng J Med 232:432-434, 1945

DR JOE V MEIGS Is it not true, however, that patients with pelvic inflammatory disease frequently have follicular cysts of the ovary and fall into the group of patients that simulate metropathia, without amenorrhea, followed by bleeding? Is that not characteristic, particularly with chronic pelvic inflammation?

DR STURGIS That is why we did not pay too much attention to the irregularity.

DR MEIGS Dr Younge, do you agree that this case is consistent with the picture one sees with chronic pelvic inflammation?

DR PAUL A YOUNGE Yes

DR MALLORY Will you describe the operative findings Dr Sturgis?

DR STURGIS Operation disclosed a tubo-ovarian mass plastered to the uterus, with dense adhesions. In view of the previous history of five years of inflammation we believed that a hysterectomy was indicated. That is the reason for the removal of the uterus, as well as the mass, which we did not open at operation. We did not suspect anything more than inflammation when the operation was performed.

DR SIMMONS Had the right ovary and the appendix been left in at the first operation?

DR STURGIS The ovary had not been removed, but I cannot remember about the appendix.

DR SIMMONS Was an Aschheim-Zondek test done?

DR MALLORY No

CLINICAL DIAGNOSIS

Tubo-ovarian abscess

DR SIMMONS'S DIAGNOSIS

Ectopic pregnancy, left fallopian tube

ANATOMICAL DIAGNOSES

Acute and chronic salpingo-oophoritis

Placental polyp

PATHOLOGICAL DISCUSSION

DR MALLORY The tubo-ovarian mass was a purely inflammatory lesion, but on opening the uterus we found a small reddish polypoid mass in the fundus, which proved to be a placental remnant. The patient had been pregnant, but it had been an intrauterine rather than an extrauterine pregnancy.

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

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MATERIAL should be received not later than noon on Thursday three weeks before date of publication.

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PNEUMOCOCCAL PNEUMONIA

MANY physicians with long experience have been unimpressed with the steady decline in the occurrence of pneumococcal pneumonias in recent years. Although reliable figures of incidence are not available, it is apparent from mortality statistics either that the disease has become less frequent or milder or that modern general management has become increasingly effective, because the decline in mortality antedates the widespread use of recent antibacterial therapy. In Massachusetts, for example, there was a decline of almost 50 per cent in the death rate from pneumonia between 1920 and 1930, as compared with the fairly stable rates recorded in the two preceding decades.¹ In more recent years the drop in mortality has been even more striking. Thus, the deaths from all forms of pneumonia per 100,000 industrial policyholders was 69.8 in 1936, 44.6 in 1940

and 25.9 in 1946, having been 115.2 in 1911.² In the last decade, moreover, pneumonia of all forms (mostly pneumococcal pneumonia) has dropped from third to eighth place among the leading causes of death.³

Unfortunately, accurate figures dealing specifically with large groups of patients with pneumococcal pneumonia are becoming increasingly difficult to assemble. The wide therapeutic range of sulfonamides and penicillin offers too little incentive for the effort required to do careful bacteriologic studies, including pneumococcus typing. Furthermore, these forms of therapy are now generally applied early, as they should be, but bacteriologic studies are all too often undertaken only when the results of therapy do not seem to come up to the physician's expectations. By that time the bacteriologic results may be vitiated by the effects of therapy.^{4,5}

It may not be amiss to point out that it is still important to carry out or at least to obtain materials for bacteriologic studies before treatment with antibacterial agents is begun. The results may prove helpful both in prognosis and in the conduct of the therapy. Although pneumococcal pneumonia can be diagnosed from clinical findings with considerable accuracy,⁶ this may not be true early in the disease, when treatment is most effective both in saving life and in preventing serious complications. The management varies appreciably when a staphylococcus, Friedländer bacillus or *Haemophilus influenzae* is the causative organism. Staphylococcal pneumonias require larger doses of penicillin, and treatment must be continued longer than in pneumococcal cases. The other two forms may not be frequent, but their seriousness, their failure to respond adequately, if at all, to sulfonamides and penicillin and the availability of streptomycin, which may be highly effective if properly used, make it essential to recognize them as early as possible. This can be done only bacteriologically. Gram-stained smears of sputum are simple to make and offer the easiest and fastest means of recognizing the less frequent forms of bacterial pneumonia. The results can then be confirmed by routine cultures. Blood and sputum should therefore be obtained for that purpose before treatment is started, but therapy need not be delayed until the results are available.

A Wright-stained smear of the sputum may also give useful information. The predominance or presence in appreciable numbers of either eosinophils or mononuclear cells, especially if bacteria are absent or scant, suggests a nonbacterial etiology. Eosinophils point to either a parasitic or an allergic agent, and mononuclears, to a viral infection. In either event the failure of antibacterial therapy can thereby be predicted or explained.

The treatment of the patient as a whole, with all his symptoms and manifestations, is still highly important in pneumococcal pneumonia. This is particularly true in infants, in the aged and in those who are severely ill or have serious complications, such as congestive heart failure. One can take little solace from the fact that autopsy reveals no evidence of residual active infection following proper antibacterial therapy in a patient who died of some physiologic disturbance whose correction might have resulted in recovery.

Regarding the optimum specific therapy for pneumococcal pneumonias there is evidence that penicillin is slightly more effective than sulfonamides when used separately⁷ and that both agents, either combined or used to supplement one another, are somewhat more effective than either agent alone.^{8,9} The latter conclusion is based on observations with what may now be considered small doses of penicillin, there being no adequate reports on the use of large doses. For adults, doses equivalent to 30,000 units or more intramuscularly every three hours in early and uncomplicated cases of moderate severity, or up to 100,000 units every three hours in severe bacteremic cases, especially when there are hidden or manifest purulent complications, may give effects that cannot be improved on by the addition of sulfonamides. In meningitis, however, the use of a sulfonamide as an adjunct is probably essential. The possibility of infections with penicillin-resistant strains is still only hypothetical, and sulfonamides would become essential if that eventuality arose. Theoretically, specific antipneumococcus serums should also be helpful, but that has not proved to be true in practice.³

Lest the wrong impression be created, it should be emphasized that the doses of penicillin mentioned are far in excess of those required by the great ma-

jority of patients. For them, as little as 15,000 units intramuscularly every three hours is adequate. The larger doses are needed for the sickest patients, among whom the fatalities are likely to occur. It should be added that oral penicillin in doses of 50,000 or 100,000 units every two or three hours, with care to avoid giving them within one and a half to two hours after a meal, is effective in most cases of moderate severity.^{10,11} Oral therapy may also prove useful in infants and children.¹² Furthermore, daily intramuscular injections of 300,000 units in peanut oil and beeswax may also give a satisfactory result in the average case. In moderately or severely sick patients, however, oral doses cannot be relied on, and the oily preparation should probably not be used or should be given twice a day until the infection has been completely controlled. In all cases, treatment should be continued after apparent recovery with the same or somewhat smaller doses for three to five days, and longer when there are complications.

Repeated local instillations of penicillin into purulent foci afford the most effective therapy for purulent complications, whenever feasible. As much as 50,000 units or even more may be instilled in 10 cc of physiologic saline solution intraspinally or into a joint, and up to 300,000 units in 50 to 100 cc of saline solution may be given intrapleurally each time, the instillations being continued daily in most cases until the infection is well under control. Much smaller doses, however, are usually adequate. Operative drainage can thus be avoided in the majority of cases of empyema.¹³ Systemic therapy is continued, in addition, if the pulmonary infection has not been fully controlled.

The case fatality rates in cases of pneumococcal pneumonia properly treated with sulfonamides and penicillin is now almost zero in young and middle-aged adults and has been reduced to 10 or 15 per cent in those over forty years of age.^{7-9,14}

REFERENCES

- 1 O'Hara, D. *Air-borne Infection. Some observations on its decline*. 114 pp. New York: The Commonwealth Fund, 1943. P. 52.
- 2 Metropolitan Life Insurance Company. Record low mortality in 1946. *Statistical Bull.* 28:15, 1947.
- 3 *Ibid.* Thirty-five years of progress in reducing mortality. *Ibid.* 27:3-7, 1946.
- 4 Goodwin, R. A., Jr., Wilcox, C. and Finland, M. Persistence of pneumococci in sulfonamide treated cases of pneumonia. *Am. J. Hyg.* 62:628-639, 1945.
- 5 Ory, E. M., Harris, H. W., Meads, M., Wilcox, C., and Finland, M. Bacteriologic studies of sputum in patients with pneumococcal pneumonia treated with penicillin. *J. Lab. & Clin. Med.* 31:409-422, 1946.

- 6 Finland, M. Pneumonia etiology, diagnosis and specific treatment *Am J Med* 1 507-517, 1946
- 7 Kinsman, J. M., et al. Treatment of pneumonia with sulfonamides and penicillin *J A M A* 128 1219-1224, 1945
- 8 Collen, M. F., Sellers, A. L., and Kast, E. C. Combined penicillin and sulfadiazine therapy in pneumococcal pneumonia *Am J M Sc* 211 299-306, 1946
- 9 Dowling, H. F., Hussey, H. H., Hirsh, H. L., and Wilhelm, F. Penicillin and sulfadiazine, compared with sulfadiazine alone in treatment of pneumococcal pneumonia *Ann Int Med* 25 950-956 1946
- 10 Bunn, P. A., McDermott, W., Hadley, S. J., and Carter, A. C. Treatment of pneumococcal pneumonia with orally administered penicillin *J A M A* 129 320-327, 1945
- 11 Finland, M., Meads, M., and Ory, E. M. Oral penicillin *J A M A* 129 315-320, 1945
- 12 Henderson, J. L., and McAdam, I. W. J. Oral administration of penicillin to infants *Lancet* 1 922-925, 1946
- 13 Brown, B., Ory, E. M., Meads, M., and Finland, M. Penicillin treatment of empyema: report of 24 cases and review of literature *Ann Int Med* 24 343-370 1946
- 14 Kaske, G. J. 1265 pneumonia cases with no deaths *U S Nav M Bull* 46 731-735, 1946

THE VALUE OF WELL DIRECTED ENDEAVOR

ANNUAL reports are generally written for public consumption. Reading the reports of philanthropic foundations that spend in excess of a million dollars each year may lead one to contemplate the validity of their work—for it is fully as difficult to spend money usefully as it is to make it honestly. Occasionally, the report of a great foundation is tinctured by a sense of humility, and the smallness and the ineffectiveness of what a mere million dollars can buy are thus apparent. The twenty-eighth annual report of the Commonwealth Fund is an example.

The bridge is seldom made between what needs to be done on a large scale and what may be demonstrated in a small pilot study. This is not because the disproportions are so great but rather because the conditions, raw materials and general circumstances cannot be reproduced for the larger applications. We do not fail because we have not been shown how to do things better but because we cannot reproduce in volume the selected circumstances under which we make the initial experiment. Unless we can conduct the trial studies with the same raw materials with which they will later have to be enlarged, we work in ivory towers, however interesting the interiors of these towers may be to the privileged few, the world outside is steered by larger masses. Most foundation boards would agree that the late William H. Welch was an outstanding contributor to the welfare of mankind, but in the recent biography of Harvey Cushing it is related that a Mr. Johnson, Welch's home-town pharmacist, although admitting that "Willy did pretty well down south in Baltimore," thought that he never compared

with his father, a country doctor. There are many more Mr. Johnsons voting than there are directors of foundations, and the experiments of the latter may not be convincing enough to be implemented by the masses on a large scale.

Educators universally encourage the idea that each individual can by aspiration and perspiration raise himself to the top, but their tongues are in their cheeks, with Robert Schumann, they know that "nature would burst should she attempt to produce nothing save Beethovens." Educational institutions also proclaim, with institutional tongues in their cheeks, that they create leaders. They do nothing of the sort. Leaders are born to flourish, some in one environment and some in another, and in a variable but small ratio to the numbers of people whom they lead. An institution that points with pride to its shaping of men's lives is like a person pointing with pride to his parents as if he had personally selected them. Institutions do try to select, but they make conspicuous mistakes and they cannot predict.

Society has an evolving pattern of growth. It seems destined to follow false prophets until it is on the brink of disaster, when the almost superhuman leadership necessary to turn it back toward normal appears. It never quite gets back, however, because there is no agreement about normality. What was normal yesterday is abnormal today, and tomorrow's normal is still different from today's. Is our halting progress due to the fact that we plan on a normality that is evanescent?

In its twenty-eighth annual report, the Commonwealth Fund asks such questions, and it answers them hypothetically by concluding that it is not *how much* it does but what *kind* of things it lays its hand to that really matters.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

O'HALLORAN—William T. O'Halloran, M.D., of Newtonville, died March 21. He was in his forty-ninth year. Dr. O'Halloran received his degree from Tufts College Medical School in 1924. He was assistant professor of medicine at Boston University School of Medicine, and physician-in-chief, Sixth Medical Service, Boston City Hospital. He was a member of the American College of Physicians, the American Heart Association and the New England Heart Association and a fellow of the American Medical Association. His mother, his widow, a son and five sisters survive.

SANDLER—Frank F Sandler, M.D., of Revere, died March 24. He was in his fifty-seventh year.
Dr Sandler received his degree from Tufts College Medical School in 1915. He was a member of the American Society of Anesthetists and a fellow of the American Medical Association.

His widow, two sons and a daughter survive.

TAYLOR—Lois E Taylor, M.D., of Belchertown, died March 21. She was in her thirty-eighth year.

Dr Taylor received her degree from University of Vermont College of Medicine in 1933. She was a member of the New England Society of Psychiatry and the New England Pediatric Society.

Her father and four brothers survive.

MEDICOLEGAL ABSTRACT

Unauthorized Practice Right of dentist injured by competition of unlicensed practitioner to obtain a court order to prohibit it. A recent New Jersey decision clarifies the function of statutes limiting the right of professional practice to licensed practitioners and the rights that the license confers on them. Two licensed dentists and an association of several licensed dentists sought to enjoin an unlicensed dentist from continuing to practice. The New Jersey statute provided that no one should practice dentistry in that state unless licensed to do so by the State Board of Registration and Examination. The statute provided a money penalty, and a supplement to the statute permitted the Attorney General or the State Board of Dentistry to bring suit to enjoin practice by an unlicensed dentist. The suit was not brought by the Attorney General or the State Board but by licensed dentists who complained that they were losing business and fees because of the unfair and illegal competition of the defendant. They claimed the right to be free from competition from a person practicing without a license.

The court rejected this claim, saying

Prior to the enactment of the dentistry statute no such property right existed. Whether the statute created such right depends upon the purpose for which it was enacted.

I think that the statute in question was passed solely for the protection of the public as against incompetents, and whatever financial benefit results to persons licensed thereunder by the exclusion of unlicensed persons from practicing dentistry is merely incidental, and that the statute was not intended to vest a property right in one licensed thereunder which the licensee is entitled to have protected by a suit of this nature.

The court thus gives a broad indication that a licensed practitioner who is injured by the competition of an unlicensed practitioner has no right on his own initiative, unless the statute gives him one, to have a court eliminate that competition. If the public board or organization cannot be persuaded to take the action they are authorized to take, the injured practitioner has no remedy.

It is well to bear in mind that the statute or circumstances governing another profession or applicable in another state may give the injured practitioner the right that the court holds the New Jersey dentist did not have (*Lipman v Forman*, 138 New Jersey Eq 556).

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

NEW LOCATION OF ANTIPNEUMOCOCCUS SERUM DEPOT

The present procedure for issue of antipneumococcus serum by the Department of Public Health was summarized in the December 12 issue of the *Journal*. The following change has arisen since that time because of the removal of the Bacteriological Laboratory from the State House, the supply of antipneumococcus serum has been transferred to the Division of Biologic Laboratories. Supplies of antipneumococcus serums, Types 1 to 33, inclusive, may be obtained, under the conditions described in the previous notice, from the Division of Biologic Laboratories, 375 South Street, Jamaica Plain 30 (telephone, ARNold 4127). Emergency service is available at all hours.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR FEBRUARY, 1947

DISEASES	RÉSUMÉ		
	FEBRUARY 1947	FEBRUARY 1946	SEVEN-YEAR MEDIAN
Chancroid	2	1	1*
Chicken pox	2544	765	1340
Diphtheria	58	21	13
Dog bite	558	487	511
Dysentery, bacillary	13	9	9
German measles	101	216	188
Gonorrhea	346	494	326
Granuloma inguinale	1	0	0*
Lymphogranuloma venereum	2	1	1*
Malaria	8	102	5
Measles	2021	1142	1753
Meningitis, meningococcal	9	19	19
Meningitis, Pfeiffer bacillus	4	2	2
Meningitis, pneumococcal	5	4	4†
Meningitis, staphylococcal	1	0	0†
Meningitis, streptococcal	0	0	0†
Meningitis, other forms	2	0	0†
Meningitis, undetermined	7	5	5†
Mumps	667	639	1091
Pneumonia, lobar	128	223	356
Poliomyelitis	0	1	2
Salmonellosis	5	8	4
Scarlet fever	629	706	1201
Syphilis	271	526	374
Tuberculosis, pulmonary	205	205	192
Tuberculosis, other forms	13	11	14
Typhoid fever	0	0	2
Undulant fever	4	0	1
Whooping cough	620	410	595

*Three-year median

†Five-year median

COMMENT

Primary interest is again focused this month on diphtheria. The number of cases reported in February is nearly three times that reported during the month of February, 1946, and slightly more than four times the seven-year median. The spread into the Connecticut Valley, noted in January, is continuing and calls for prompt action on immunization in this area to check the spread. The usual seasonal decline is beginning. The highest month was December, with 86 cases, 77 cases were recorded in January.

Chicken pox has shown a sharp increase this month over February, 1946, and is about two times the seven-year median. This is the continuation of the upward swing in the cyclic rhythm that began a year ago.

Diseases above the seven-year median for the month are bacillary dysentery, measles, salmonellosis, pulmonary tuberculosis, undulant fever and whooping cough.

Among the diseases below the seven-year median are German measles, meningococcal meningitis, mumps, lobar pneumonia, poliomyelitis, scarlet fever and typhoid fever.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anthrax was reported from Milton, 1, total, 1.

Diphtheria was reported from Amesbury, 1, Boston, 35, Bridgewater, 1, Chicopee, 5, Dedham, 1, Easthampton, 3,

Holyoke, 1, Lowell, 1, Malden, 2, Medford, 1, Natick, 1, New Bedford, 2, Springfield, 2, West Bridgewater, 2, total, 58

Dysentery, amebic, was reported from Boston, 1, total, 1
Dysentery, bacillary, was reported from Worcester, 13, total, 13

Encephalitis, infectious, was reported from Brockton, 1, total, 1

Lymphocytic choriomeningitis was reported from Cambridge, 1, Worcester, 1, total, 2

Malaria was reported from Belmont, 1, Boston, 1, Bridgewater, 1, Cambridge, 1, Medford, 1, Peabody, 1, Southbridge, 1, Westfield, 1, total, 8

Meningitis, meningococcal, was reported from Boston, 3, Brookline, 1, Haverhill, 1, Lynn, 1, Somerville, 1, Waltham, 2, total, 9

Meningitis, Pfeiffer-bacillus, was reported from Boston, 1, Lowell, 1, Medford, 1, Somerville, 1, total, 4

Meningitis, pneumococcal, was reported from Billerica, 1, Boston, 1, Palmer, 1, Salem, 1, Worcester, 1, total, 5

Meningitis, staphylococcal, was reported from Springfield, 1, total, 1

Meningitis, other forms, was reported from Boston, 1, Worcester, 1, total, 2

Meningitis, undetermined, was reported from Cambridge, 2, Lowell, 1, Springfield, 1, Worcester, 3, total, 7

Salmonellosis was reported from Attleboro, 1, Auburn, 1, Haverhill, 1, Melrose, 1, Wellesley, 1, total, 5

Septic sore throat was reported from Boston, 11, Brockton, 1, Fall River, 1, Holyoke, 1, Lancaster, 1, Medford, 1, Newton, 1, total, 17

Tetanus was reported from Chelsea, 1, total, 1

Trachoma was reported from Boston, 2, total, 2

Trichinosis was reported from Boston, 1, Fall River, 1, Quincy, 1, Westport, 1, total, 4

Undulant fever was reported from Leominster, 1, Northampton, 1, Shelburne, 1, Worcester, 1, total, 4

MISCELLANY

NOTES

The following appointments to the teaching staff of Harvard Medical School were recently announced Thomas Gucker, 3rd, of Brookline (A B Princeton University 1937, M D University of Pennsylvania 1941), assistant in orthopedic surgery, Robert Pirrie Woods, of Boston (S B Yale University 1935, M D McGill University 1940), research fellow in surgery, Earl Baker Wert, of Collingswood, New Jersey (M D University of Pennsylvania 1940) assistant in pathology, Peter Hobart Knapp, of Boston (A B Harvard University 1937, M D Harvard University 1941), assistant in psychiatry, Stanley Leonard Robbins, of Brookline (S B Mass Institute of Technology 1936, M D Tufts College 1940), instructor in pathology, Albert Irwin Mendeloff, of Charleston, West Virginia (A B Princeton University 1938, M D Harvard University 1942, M P H Harvard University 1944), assistant in medicine, Curtis Prout, of Dover (A B Harvard University 1937, M D Harvard University 1941), assistant in medicine, Joseph Edward Warren, of Boston (A B Boston College 1934, M D Harvard University 1938), assistant in medicine, Mary Ochsenhirt Amdur, of Somerville (S B University of Pittsburgh 1943, Ph D Cornell University 1946), assistant in ophthalmic research, Toufic Hanna Kalil, of Manchester, New Hampshire (M D Tufts College 1931) assistant in radiology, Jean Patricia Davis, of Rockville, Missouri (A B Smith College 1939, M D Yale University 1943), research fellow in pediatrics, Aniela Stephanie Zygmuntowicz, of Uxbridge (A B Brown University 1938) research fellow in pediatrics, and Fred Ralph Zeiss, of Chicago, Illinois (A A Crane College 1926, B M Northwestern University 1930, M D Northwestern University 1931, S M Northwestern Graduate School 1931), assistant in orthopedic surgery

AUTOMOBILE LIABILITY INSURANCE

According to a letter recently forwarded to members of the Newton Chamber of Commerce, Chapter 614, Acts of 1946, entitled "An Act Relative to Action for Death and Injuries Resulting in Death," drastically changes the present limit of damages in suits for wrongful death. Previous to the passing of this act, which became effective January 1, 1947, the limit

of damages that could be recovered in a suit for the negligent cause of death to a person was \$10,000. This was amended by the 1946 General Court by increasing the amount to \$15,000. In addition, a right is given to sue for "conscious suffering" preceding death. Damages for death are assessed on the degree of culpability of the person causing the death by his negligence, and also according to the pecuniary loss sustained to the parties entitled to benefit by the suit. Previous to this change in the law, damages were assessed according to the degree of culpability only. As a result, it is possible that a motorist in Massachusetts who is involved in an accident in which a person is fatally injured, may find himself liable for damages amounting to \$15,000 or \$20,000.

Since the statutory amount of compulsory insurance remains the same, — that is, \$5,000 liability for damages to any one person, and \$10,000 for each accident, — the average motorist will not be afforded sufficient financial protection by that type of policy. Insurance companies that carry liability coverage are therefore recommending to their policy holders an increase in the amount of liability to \$15,000 for damages to any one person and \$30,000 for damages arising out of any one accident.

BOOKS AND WORLD RECOVERY

The desperate and continued need for American publications to serve as tools of physical and intellectual reconstruction abroad has been made vividly apparent by appeals from scholars in many lands. The American Book Center for War Devastated Libraries has been urged to continue meeting this need at least through 1947. The Center is therefore making a renewed appeal for American books and periodicals — for technical and scholarly books and periodicals in all fields and particularly for publications of the past ten years. Complete or incomplete files of the *New England Journal of Medicine* will be especially welcome.

The generous support that has been given to the Center has made it possible to ship more than 700,000 volumes abroad in the past year. It is hoped to double this amount before the Center closes. The books and periodicals that personal or institutional libraries can spare are urgently needed and will help in the reconstruction that must preface world understanding and peace.

Contributions should be sent to the American Book Center, c/o The Library of Congress, Washington 25, D C, freight prepaid.

BOOK REVIEWS

Preventive Medicine and Public Health. By Wilson G Smillie, M D, D P H, Sc D (hon.) 8°, cloth, 607 pp., with 41 illustrations and frontispiece and 21 tables. New York: Macmillan Company, 1946. \$6.00.

This text gives an excellent summary of the present-day activities of physicians and public-health agencies in the battle against disease, the amelioration of physical and mental handicaps and the promotion of positive health. The picture is painted with broad strokes and with only enough detail to give an adequate understanding of both the problems and the best recognized methods of solution. This makes it possible to cover a wide scope and yet to keep the text handy in size.

The author is a man who has devoted his life to a career in public health, both as a health officer and later as an outstanding teacher, first in Brazil and then at the Harvard School of Public Health and Cornell University Medical College. His interest in field studies did not cease with the beginning of his teaching career. Contributions to epidemiology and public-health administration continue to come from his pen.

Massachusetts readers will recognize the author's loyalty to a pioneer in public health in the quotations from Lemuel Shattuck's report on the sanitary condition of Massachusetts (1850) that grace the beginning of each section. The modern sound of the quotations reminds one of the broad scope of the thinking of the commission that Shattuck headed.

Some specialists will believe that certain sections do not give the latest word regarding their own special field. The terminology is often not the latest. These are inevitable shortcomings of textbooks of broad scope because one man, even with the considerable assistance obtained by the author, cannot be expected to be familiar with the intimate details

of the many special fields. The typographical and editorial errors seem to have been kept at the minimum.

The book not only is valuable in orienting the medical student in preventive medicine but also is a mine of information for the practicing physician and the public-health worker. It will be useful in suggesting sources of public services that patients are often unable to provide for themselves. It should be on the desk of every physician. The readable style, logical arrangement, useful illustrations and excellent type and paper make it a pleasure to use the book.

Hippocratic Wisdom. For him who wishes to pursue properly the science of medicine. A modern appreciation of ancient scientific achievement. By William F Petersen, MD S°, cloth, 263 pp. Springfield, Illinois: Charles C Thomas, 1946 \$5.00

This thoroughly fascinating and scholarly volume is a modern interpretation of ancient scientific achievement, a commentary and interpretation of the Hippocratic texts in the light of present knowledge, for those who wish to pursue properly the study of medicine. The author is particularly interested in the relations of climate and seasons to human disease, and their influence on clinical phenomena. Beginning with "Airs, Waters and Places," he reviews the principal works of Hippocrates, and illustrates their sagacity and truth by applying them to actual case histories of erysipelas, anoxia, miscarriage, epilepsy, rabies, pneumonia, pleurisy, empyema, phthisis, bone tuberculosis, appendicitis, talipes, tetanus and many others. Nearly everything that modern medicine has discovered was foreshadowed, at least *in posse*, by the Hippocratic wisdom. Moreover, the author emphasizes the fact that, in both the theory and the practice of physic, Hippocrates always viewed his problems in the light of the concept of the whole man, not of the disease as a so-called "clinical entity." Only recently has it been realized that from this standpoint alone can disease in human beings be properly appreciated and understood.

Dr Petersen's work is illustrated by an abundance of well chosen figures in the text. It is also illuminated by copious notes gathered into an appendix, which constitutes an invaluable commentary on the text. Finally, there are many bibliographic references, ancient and modern, a glossary and indexes of illustrations and contents. In modest compass, this is a monumental and inspiring book.

Ophthalmology in the War Years. Edited by Meyer Wiener, MD. Volume I 1940-1943. 8°, cloth, 1166 pp. Chicago: Year Book Publishers, Incorporated, 1946. \$13.50

With the support of the National Research Council and through the efforts of a committee under the leadership of Dr Meyer Wiener, with thirty-six able contributors, the ophthalmologic literature of the world during the war years is brought to the elbow of practicing ophthalmologists in the form of two volumes. Volume I reviews over eighty-five hundred important articles published during the years 1940-1945. Volume II, in press, will cover the period 1944-1946. Thus, the ophthalmologists who served in the armed forces and those who served at home are given an unparalleled opportunity to catch up with the advances in ophthalmology.

Great commendation is due the contributors of this valuable review, to the National Research Council and to the publishers for bringing such an important aid and stimulus to the ophthalmologic profession. Every progressive ophthalmologist will either buy these volumes for his working library or combine with his colleagues to obtain the volumes for his local medical library.

Technique of Psychoanalytic Therapy. By Sandor Lorand, MD. 8°, cloth, 251 pp. New York: International Universities Press, 1946. \$3.50

This volume is based on talks that the author has given, especially those at the New York Psychoanalytic Institute. Although it is admitted in the preface that therapeutic achievement may be arrived at "through different avenues of approach," the text follows closely the Freudian school, including dream interpretations, oedipus complex and the couch. If the reader is not orthodox—that is, a heretic—he will find time to do considerable day-dreaming himself while perusing the pages. If one is orthodox, reading will be unnecessary.

The linking of physiologic forces with the psychologic is admitted only because it helps the patient to understand his symptoms.

One patient who fell asleep during the analytical hour is stated to have been expressing "his strong defense against change and fear that his defenses would be broken." Here the interpretation of the psychology of sleep will be new to psychiatrists who have been compelled to give sedatives for the induction of sleep to overcome "defense against change and fear."

"Character neurosis" is not defined clearly but apparently applies to neurotic patients who have resistance to analysis. In dream analysis the author quotes dreams that appear to be unusual to one who has dreamed and who has listened to other people's dreams, and it is stated that "usually there are no indications of feelings in dreams or, if present, they are milder than the patient's actual, repressed feeling associated with the unconscious, latent desire."

The final chapter, on termination of analysis, could not, of course, have given explicit directions. This is a moot problem, even among psychoanalysts.

Report on a Survey of Medical Education in Canada and the United States. By C E Dolman, M R C S (Eng), L R C P, M B, B S, M R C P, D P H, Ph D (Lond), and F A P H A. 4°, paper, 53 pp., with 2 tables. Toronto: University of Toronto, 1946.

Something of the character of the author of this pamphlet is revealed by his biography as reported in *American Men of Science*. He is an Englishman educated in London who has acquired the degrees of Bachelor of Medicine, Bachelor of Science, Doctor of Public Health and Doctor of Philosophy. He worked first as house surgeon and later in research at Saint Mary's Hospital, then he came to Canada, where he engaged in further research at the Connaught Laboratory in Toronto. Finally he moved to Vancouver, where he is now professor of bacteriology and preventive medicine in the University of British Columbia, as well as director of the Provincial Board of Health Laboratories. This record speaks for his industry and competency.

A little over a year ago he was instructed by the Board of Governors of his university to survey medical education in the United States and Canada. He approached the task by visiting eleven representative Canadian schools and twenty-two in the United States. He talked with medical educators as he met them, he received many interesting and varied impressions, and he developed a clear-cut picture in his mind of the main principles and prerequisites of a first-class school. This picture he now attempts to describe in writing.

He emphasizes several points that most medical educators would also stress: the need of university sponsorship for a medical school, of adequate budget and hospital facilities and of a strong faculty guided by a competent dean.

The author is particularly impressed with the need for a school to be intimately associated with a university, to assure, as he expresses it, physical contiguity and spiritual affinity between the faculty of medicine and other university faculties. He believes, with equal firmness, in full-time clinical teaching, the university having complete control of a sufficient number of hospital beds to ensure proper teaching facilities. In his own locality he wishes his school to exert a generally helpful educational influence by providing postgraduate training for practitioners, by improving hospital standards and by developing a close relation with city and provincial health departments.

The report is written intelligently. As the author says, it is likely to be approved in general by educators. Yet, he adds, he is certain that his suggestions will meet strong opposition from certain quarters. He hints that it may be difficult to obtain sufficient funds from the purses of the people to develop and finance a thoroughly sound program of medical education. Good medical education is costly, and not everyone sees the need for it.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Diseases of the Skin. By George C Andrews, MD, associate clinical professor of dermatology, Columbia University College of Physicians and Surgeons, chief of clinic, Department of Dermatology, Vanderbilt Clinic, chief, Derma-

tology Clinic, Roosevelt Hospital, attending dermatologist, Presbyterian Hospital and Roosevelt Hospital, and consulting dermatologist and syphilologist, Tarrytown Hospital, Grasslands Hospital, Valhalla, St. John's Hospital, Yonkers, Greenwich Hospital and Beckman-Downtown Hospital Third edition 8°, cloth, 937 pp, with 971 illustrations Philadelphia and London W B Saunders Company, 1946 \$10 00

Public Health and Welfare Reorganization The postwar problem in the Canadian provinces By Harry M Cassidy, Ph D 8°, cloth, 464 pp Toronto The Ryerson Press, 1945 Cloth, \$4 50, paper \$3 50

Muscle Testing Techniques of manual examination By Lucille Daniels, M A, director and associate professor of physical therapy, Stanford University, Marian Williams, M A, assistant professor of physical therapy, Stanford University, and Catherine Worthingham, M A, director of professional education, National Foundation for Infantile Paralysis, Incorporated 4°, paper, 189 pp Designed and illustrated by Harold Black, with 349 diagrammatic line drawings Philadelphia and London W B Saunders Company, 1946 \$2 50

Electrocardiography in Practice By Ashton Graybiel, M D, Captain, Medical Corps, United States Naval Reserve, coordinator of research, United States Naval School of Aviation Medicine, Pensacola, Florida, and Paul D White, M D, lecturer in medicine, Harvard Medical School, and physician, Massachusetts General Hospital With the assistance of Louise Wheeler, A M, executive secretary, Cardiac Laboratory, Massachusetts General Hospital, and Conger Williams, M D, assistant in medicine, Harvard Medical School and Massachusetts General Hospital Second edition 8°, cloth, 458 pp, with 323 illustrations Philadelphia W B Saunders Company, 1946 \$7 00

Injury and Death under Workmen's Compensation Laws The fundamental principles as interpreted by the courts and compensation experts in all compensation states and in other jurisdictions, including the American territories and England By Samuel B Horowitz, A B, LL B 8°, cloth, 486 pp Boston Wright and Potter Printing Company, 1946 \$6 00

Electrocardiography, including an atlas of electrocardiograms By Louis N Katz, M D, director of cardiovascular research, Michael Reese Hospital, Chicago, and professorial lecturer in physiology, University of Chicago School of Medicine Second edition, thoroughly revised 4°, cloth, 882 pp, with 525 illustrations Philadelphia Lea and Febiger, 1946 \$12 00

Nursing in Commerce and Industry By Bethel J McGrath, R.N., for the National Organization for Public Health Nursing 8°, cloth, 356 pp New York Commonwealth Fund, 1946 \$3 00

Sex, Marriage and Family By Thurman B Rice, M.D., professor of bacteriology and public health, Indiana University School of Medicine 8°, cloth, 272 pp Philadelphia J B Lippincott Company, 1946 \$2 50

Fees and Fee Bills Some economic aspects of medical practice in nineteenth century America By George Rosen, M.D., Ph D Supplement No 6 to the Bulletin of the History of Medicine. 4°, paper, 91 pp Baltimore Johns Hopkins Press, 1946 \$1 50

Water Treatment and Purification By William J Ryan, M E Second edition 8°, cloth, 270 pp, with 66 illustrations New York and London McGraw-Hill Book Company, Incorporated, 1946 \$2 75

Women in Industry Their health and efficiency By Anna M Baetjer, Sc D, assistant professor of physiological hygiene, School of Hygiene and Public Health, Johns Hopkins University Issued under the auspices of the Division of Medical Sciences and the Division of Engineering and Industrial Research, National Research Council Prepared in the Army Industrial Hygiene Laboratory 8°, cloth, 344 pp, with 122 tables Philadelphia and London W B Saunders Company, 1946

NOTICES

ANNOUNCEMENTS

Dr John K. Brines announces the removal of his office to 619 Washington Street, Wellesley

Dr Arthur W Clancy has returned from military service and has resumed practice at 102 High Street, Newburyport, specializing in diseases of the eye, ear, nose and throat.

Dr Henry W Ohrenberger announces the opening of his office at 1101 Beacon Street, Brookline, for the practice of gynecology and obstetrics

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Tuesday, May 6, at 8 15 p m Dr Willem J Kolff, chief of the Department of Medicine, Municipal Hospital, Kampden, Holland, will speak on the subject "New Ways of Treating Uremia"

AMERICAN CONGRESS OF PHYSICAL MEDICINE

The twenty-fifth annual scientific and clinical session of the American Congress of Physical Medicine will be held September 2 to 6, inclusive, at the Hotel Radisson, Minneapolis Scientific and clinical sessions will be given on September 3, 4, 5 and 6 All sessions will be open to members of the medical profession in good standing with the American Medical Association In addition to the scientific sessions the annual instruction courses will be held September 2, 3, 4 and 5 These courses will be open to physicians and therapists registered with the American Registry of Physical Therapy Technicians

For information concerning the convention and the instruction course, address the American Congress of Physical Medicine, 30 North Michigan Avenue, Chicago 2

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, APRIL 24

FRIDAY, APRIL 25

*9-00-10-00 a m Temporal Arteritis Dr Roy C Crosby Joseph H Pratt Diagnostic Hospital

*10-00 a m-12-00 m Medical Staff Rounds. Peter Bent Brigham Hospital.

MONDAY, APRIL 28

*12-15-1-15 p m Clinicopathological Conference Peter Bent Brigham Hospital

TUESDAY, APRIL 29

12-00 m-1-00 p m Dermatological Service, Grand Rounds. Amphitheater, Dowling Building, Boston City Hospital

*12-15-1-15 p m Clinicorontgenological Conference Peter Bent Brigham Hospital.

WEDNESDAY APRIL 30

*9-00-10-00 a m The Relation of Enzyme Chemistry to Some Recent Advances in Chemotherapy Dr Gerhardt Schmidt. Joseph H Pratt Diagnostic Hospital

*11-00 a m-12-00 m Medical Clinic Amphitheater Children's Hospital

*12-00 m Clinicopathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital

*2-00-3-00 p m Combined Clinic by the Medical, Surgical and Orthopedic Services Amphitheater Children's Hospital

*Open to the medical profession

APRIL 22 Cutter Lecture Page 554 issue of April 10

APRIL 26-MAY 4 Industrial Health Meetings Page 456, issue of March 20

APRIL 28-MAY 2 American College of Physicians Page 206 issue of August 8

MAY 6 Greater Boston Medical Society Notice above

MAY 8 Cerebral Hemorrhage Dr Raymond Adams Pentucket Association of Physicians 8:30 p m Haverhill

MAY 9 Boston University School of Medicine Alumni Association Page 554 issue of April 10

MAY 19-22 Massachusetts Medical Society Annual Meeting Hotel Statler, Boston

(Notices continued on page xix)

The New England Journal of Medicine

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Volume 236

APRIL 24, 1947

Number 17

STREPTOMYCIN TREATMENT OF PULMONARY INFECTIONS*

Clinical and Bacteriologic Studies of Six Cases

H WILLIAM HARRIS, M.D.,† RODERICK MURRAY, M.D.,‡ TOM F. PAINE, M.D.,§
AND MAXWELL FINLAND, M.D.¶

BOSTON

ALTHOUGH pulmonary infections caused by gram-negative bacilli are much less frequent than those caused by gram-positive cocci, they are generally severe and often leave serious damage in the lungs of patients who recover. Their importance has become particularly evident since the advent of the sulfonamides and penicillin, which have produced highly favorable results in pneumococcal, streptococcal and staphylococcal pneumonias but have not materially influenced those due to gram-negative bacilli.

Since the original report by Schatz, Bugie and Waksman¹ on streptomycin and its antibacterial action against certain gram-negative bacilli, numerous studies have confirmed the marked effect of this antibiotic against most gram-negative bacteria including those that cause pulmonary infections.²⁻⁷ There are few reports, however, on the clinical use of streptomycin in pulmonary infections. Herrell and Nichols⁸ treated 5 cases of suppurative disease of the tracheobronchial tree caused by a variety of gram-negative organisms, and obtained good results in 4. Olsen⁹ mentioned briefly the successful use of the antibiotic by nebulization in 9 patients with bronchiectasis who had not responded to penicillin therapy and whose sputums contained a variety of gram-negative organisms. He pointed out that, whereas streptomycin treatment often

eliminated gram-negative organisms from the sputum and thereby reduced both the cough and the volume of sputum, the primary bronchial dilatation was not affected and the patients were still subject to the hazards of a deformed bronchial tree. Durant and his associates¹⁰ reported 3 cases of pulmonary infections caused by *Haemophilus influenzae* that were treated by bronchoscopic instillation of streptomycin, supplemented in one case by parenteral administration. The results were uniformly good. The successful use of streptomycin in the treatment of single cases of pneumonia due to Friedländer bacillus has been reported by Learner and Minnich¹¹ and by Bishop and Rasmussen.¹² The series reported by the Committee on Chemotherapeutics and Other Agents of the National Research Council¹³ includes 44 cases of acute or chronic pulmonary infections caused by various susceptible gram-negative bacteria in which 15 patients recovered, 18 improved and 11 showed no effect from streptomycin therapy. The clinical and bacteriologic observations in 6 cases of pulmonary infections treated with streptomycin are the subject of the present report.

MATERIALS AND METHODS

Patients were chosen for treatment with streptomycin from among regular admissions to the adult medical wards of the Boston City Hospital. They all had acute or chronic bronchopulmonary infections, or both, with various gram-negative bacilli as the only or predominating organisms in the sputums. In each case the organisms obtained before streptomycin treatment were sensitive to concentrations of this antibiotic that could usually be maintained in the plasma. Three patients had acute pneumonia, and the other 3 had chronic bronchopulmonary infections with acute exacerbations. One of the

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School.

†Fellow of the streptomycin used in this study was furnished by the National Research Council from supplies assigned for clinical investigations.

‡Funded by the Committee on Chemotherapeutics and Other Agents. This study was aided in part, by a grant from the United States Public Health Service.

§Research fellow in medicine, Harvard Medical School; research fellow, Thorndike Memorial Laboratory, Boston City Hospital.

¶Research fellow in medicine, Harvard Medical School; research fellow, Thorndike Memorial Laboratory, Boston City Hospital.

††Associate professor of medicine, Harvard Medical School; chief, Fourth Medical Service and associate physician, Thorndike Memorial Laboratory, Boston City Hospital.

over the right lower lobe and there were many medium crepitant rales over both lower lobes. A systolic murmur was heard along the right sternal border. The blood pressure was 155/82. The abdomen was distended and tympanic, and there was some tenderness to deep palpation in the left upper quadrant.

Examination of the blood revealed a hemoglobin of 85 per cent (Sahli) and a white-cell count of 8600, with 53 per cent neutrophils, 40 per cent lymphocytes and 7 per cent monocytes. The blood Hinton reaction was negative. The nonprotein nitrogen of the blood was 71 mg per 100 cc. A blood culture was negative, as was urinalysis. A sputum culture showed *H. influenzae* predominating and a few colonies each of *Streptococcus viridans*, *Escherichia coli* and diphtheroids. Roentgenograms of the chest showed thickening of both hilar roots, with infiltration of the surrounding regions. There were multiple nodular areas of density throughout the right middle and both lower lobes and a larger irregular area of density in the right lower lobe. The heart was moderately enlarged, and there was an aneurysmal dilatation of the ascending aorta.

The dehydration was promptly corrected by administration of fluids parenterally, and the blood nonprotein nitrogen dropped steadily to 35 mg per 100 cc. Oxygen was given by nasal catheter with only slight improvement in the cyanosis and dyspnea, and the distention yielded only partially to repeated doses of prostigmine. Penicillin was given intramuscularly at first and then by inhalation. On the 5th day the patient became delirious and unco-operative and it was necessary to discontinue the aerosolization and to readminister the penicillin by the intramuscular route.

On the 7th hospital day the patient was still acutely ill, dyspneic, febrile and completely disoriented. At that time there were signs of consolidation in the right lower lobe and numerous rales at both lung bases. The cough was still severe and productive of large amounts of purulent sputum, cultures of which yielded a pure and abundant growth of *H. influenzae*. These organisms were also seen in large numbers in direct smears of the sputum. The organism was inhibited *in vitro* by 50 units of streptomycin per cubic centimeter. Another blood culture showed no growth.

The penicillin was then stopped, and streptomycin was started. The initial dose was 1 gm intravenously followed immediately by 1 gm intramuscularly every 6 hours for a total of 32 gm. Within 36 hours after the first dose of streptomycin the patient showed decided improvement and became rational and well oriented, and the cough and sputum diminished markedly. On the 14th hospital day, when the streptomycin was stopped, the patient's appetite had returned, and his strength had improved so that he was able to sit up in a chair for several hours each day. The signs in the lungs had also cleared progressively, and only a few crepitant rales were heard, mostly over the right lower lobe. There was irregular fever at first, with a steady rise in temperature during the last 2 days of streptomycin therapy, and a return to normal after the drug had been stopped. Direct smears and cultures of the sputum 24 hours after the first dose of streptomycin and repeatedly thereafter failed to show any *H. influenzae* bacilli. Convalescence was uneventful except for repeated episodes of urinary retention. By the end of the 3rd week the cough had completely stopped and the lungs were clear on both physical and x-ray examination.

The course, therapy and some relevant findings in this case are presented in Figure 1.

CASE 2. A 54-year-old shoemaker entered the hospital on July 3, 1946. He had had an attack of pneumonia 10 years previously and a chronic productive cough since that time. During the year before admission he noted weakness and increasing fatigue. On the day before entry he developed left- and right-sided pleuritic pain. The cough increased, and he began to raise blood-tinged sputum. The patient appeared acutely ill and dehydrated and was coughing frequently and raising tenacious rusty sputum. Dullness, bronchial breathing and crepitant rales in the right lung were the only positive physical findings. The temperature was 102°F, the pulse 100 and the respirations 25. Examination of the blood disclosed a hemoglobin of 75 per cent (Sahli) and a white-cell count of 11,500, with 86 per cent neutrophils. The blood nonprotein nitrogen was

126 mg per 100 cc. A blood Hinton test was positive. Urinalysis was negative. Microscopical examination of the stained sputum showed numerous large encapsulated gram-negative bacilli, and a culture revealed a Type A Friedländer bacillus. A blood culture showed no growth. A roentgenogram of the chest revealed dense consolidation of the peripheral portion of the right middle lobe and of the lower portion of the right upper lobe.

The antibacterial therapy and the course of the disease are shown in Figure 2. The patient was given parenteral fluids and oxygen by nasal catheter. Codeine and Demerol were used to relieve pleuritic pain. Forty thousand units of penicillin was given intramuscularly every 3 hours. On the 3rd hospital day, after adequate hydration had been obtained and the blood nonprotein nitrogen had fallen to 46 mg per 100 cc, the patient was given sulfadiazine in full doses by mouth. In spite of this therapy he showed no clinical improvement. The white-cell count increased. Friedländer bacilli persisted in large numbers in the sputum and an x-ray film of the chest showed extension of the consolidation to the remainder of the right middle and most of the right upper lobes. The penicillin and sulfadiazine were both discontinued on the 6th day, and streptomycin therapy was then begun. The initial dose was 1 gm intravenously and a similar amount intramuscularly and this was followed by 1 gm every 6 hours.

Within 48 hours, the patient appeared less dyspneic and the temperature and pulse rate dropped somewhat. A sputum culture obtained 6 hours after the initial dose of streptomycin showed only 15 colonies of Friedländer's bacillus and this organism was not found in the culture made after the 2nd day of streptomycin therapy. The gross appearance of the sputum however showed no change during this interval. A roentgenogram of the chest on the 4th day of streptomycin treatment showed no extension of the pulmonary process, but small areas of increased radiance were seen within the right middle lobe. In spite of the clinical and bacteriologic improvement the patient expired suddenly on the 4th day of streptomycin therapy after a total of 15 gm of streptomycin had been given.

Autopsy. Post-mortem examination revealed dense gravely consolidation of the right upper and middle lobes and numerous small thin-walled abscesses throughout the consolidated areas. The contents of the abscesses and the alveolar and bronchial exudate were thick mucoid and stringy and yielded Type A Friedländer bacilli on culture. No evidence of embolism was found. The organism obtained at autopsy was inhibited *in vitro* by 0.8 units of streptomycin per cubic centimeter — a value identical with the minimum inhibiting concentration before treatment.

CASE 3. A 54-year-old bartender was admitted to the hospital on September 12, 1946. A week previously he had developed a cold with coryza, and 2 days later he began to have severe pleuritic pain in the right anterior chest and a cough productive of purulent sputum. He had had pneumonia 14 years previously and two brief episodes of pleuritic pain during the preceding 4 years, but there had been no chronic cough or cardiac symptoms.

On admission the patient appeared acutely ill and in a shock-like state, the skin was flushed and moist, the tongue was dry, and the lips and fingernails slightly cyanotic. There were signs of consolidation of the lower half of the right side of the chest anteriorly, and a few medium crepitant rales were heard throughout the left posterior portion. The heart was not enlarged and no murmurs were heard, but the rhythm was totally irregular. The temperature was 98.6°F, the pulse 120 and thready, and the respirations 32 and labored. The blood pressure was 95/55.

Examination of the blood disclosed a hemoglobin of 110 per cent (Sahli), a hematocrit of 45 per cent and a white-cell count of 25,000, with 96 per cent neutrophils, half of which were young forms. The blood nonprotein nitrogen was 42 mg per 100 cc. The blood Hinton reaction was negative. The urine contained a trace of albumin and there were many fine granular casts in the sediment. An arm-to-carotid-sinus circulation time was normal and the electrocardiogram showed only auricular fibrillation.

A blood culture was positive for a Type C Friedländer bacillus*. The sputum was tenacious, purulent and bloody, and a stained smear showed it to contain innumerable large, encapsulated gram-negative bacilli and a few gram-positive lanceolated diplococci. A Neufeld test with anti-pneumococcus serums showed a reaction of some of the diplococci with Type 19 antiserum. Cultures of the sputum on blood-agar plates yielded only Friedländer bacilli, but this organism and a Type 7 pneumococcus were obtained from

after treatment were negative. Friedländer bacilli persisted in the sputum in varying numbers. Pneumococci were looked for in the sputum by all available methods. Type 7 pneumococci were isolated on only one more occasion, but Type 19 pneumococci, which had been seen in the fresh Neufeld preparation of the sputum on admission, were not observed again until they were isolated on the 8th day.

On the 5th day, signs of cavitation of the right middle lobe were made out and confirmed by x-ray study. Because of

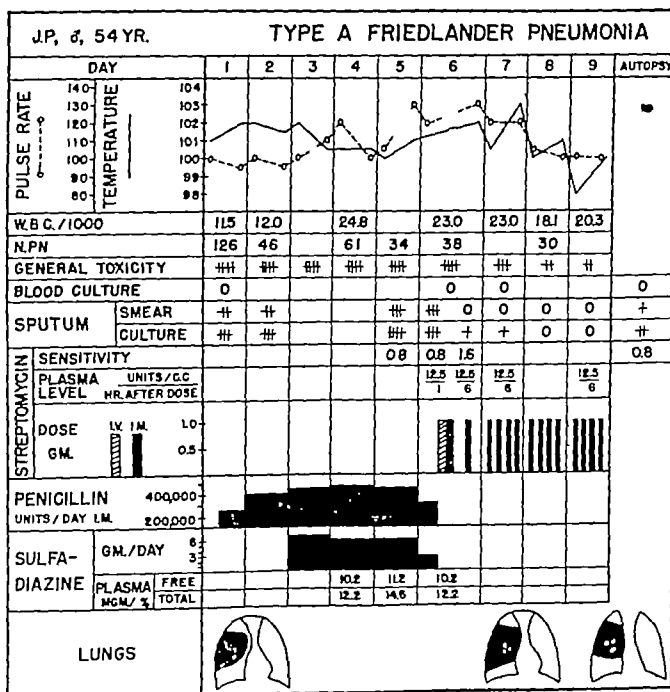


FIGURE 2 Relevant Findings in Case 2

The pneumonia progressed and organisms persisted in the sputum in large numbers during treatment with penicillin and sulfadiazine. Streptomycin therapy was followed by definite clinical improvement and elimination of Friedländer bacilli from smears and cultures of the sputum. The consolidation and abscess formation that are typical of Friedländer pneumonia were found at autopsy in the right upper and middle lobes, and moderate numbers of organisms were obtained in cultures from these lobes. No other cause of the sudden death was found.

cultures of the heart's blood of a mouse inoculated with the sputum.

The patient was given fluids parenterally and by mouth, as well as small doses of morphine and codeine to relieve the pleuritic pain, and digitalization was begun. Because of the characteristic findings in the sputum, a diagnosis of pneumonia due to a Friedländer bacillus was made, and intramuscular streptomycin was begun promptly with 1 gm every 4 hours for 2 days and then every 6 hours for 4 more days. The usual initial intravenous injection was not given in this case because of the danger that a histamine-like reaction would aggravate the shock-like state of the patient.

The therapy, course and bacteriologic findings are presented in Figure 3. The patient's general condition began to improve within a few hours. He then became progressively stronger and more active, the appetite returned, the pleuritic pain diminished, the breathing became easier and the blood pressure rose to 120/80. Auricular fibrillation continued until the 9th day, when normal sinus rhythm was restored. Blood cultures taken on four occasions during the first 2 days

this finding and because of increasing pain and tenderness at the injection sites, the intramuscular administration of streptomycin was discontinued, and subsequent doses were given by the inhalation of 125 mg dissolved in 1 cc of saline solution ten times daily. Each inhalation was preceded by a 5-minute period of postural drainage. On this regime the patient continued to improve, and the number of Friedländer bacilli in the sputum decreased. On the 10th day, because of the persistence of large numbers of Type 19 pneumococci in the sputum associated with a rising temperature, the patient was also given 100,000 units of penicillin intramuscularly every 8 hours. The temperature dropped promptly, and the number of pneumococci in the sputum diminished markedly. Both the penicillin and streptomycin were discontinued on the 17th day. At that time the patient had only a slight residual cough, raised moderate amounts of purulent sputum and had some sweating at night. Roentgenograms still showed the area of consolidation with several small abscesses.

During the next 2 months the patient remained afebrile and symptom free, and regained much weight and strength. The area of pulmonary consolidation diminished in size and showed some evidence of fibrosis. The abscesses became

*The cultures of Friedländer's bacilli in this case were all typed at the Bureau of Laboratories of the New York City Department of Health through the courtesy of Miss Annabel Walter.

radually smaller and finally could no longer be made out. Friedländer bacilli continued to be the predominant organisms in the sputum cultures, but the Type 19 pneumococci could not be isolated after the 3rd week.

The streptomycin and penicillin sensitivities of the various organisms isolated at different times during and after therapy are shown in Figure 3. The Friedländer bacilli (all the strains were Type C) increased in resistance to streptomycin abruptly and markedly on the 3rd day and remained resistant thereafter. The streptomycin sensitivity of the Type 7 pneumococcus was the same before therapy and on the 5th day.

purulent discharge from the left ear, and small perforations were seen in both tympanic membranes. Numerous crepitant rales were heard over the right middle lobe and both lower lobes of the lungs, but no signs of consolidation were made out. The sputum was profuse and mucopurulent.

Urinalysis and the hematologic findings were negative. Repeated blood Wassermann and Hinton tests were positive, but those of the spinal fluid were negative. Roentgenograms of the chest showed mottled densities of the right middle-lung field and peribronchial thickenings in both lower lobes. Films of the mastoid processes revealed thickening of the

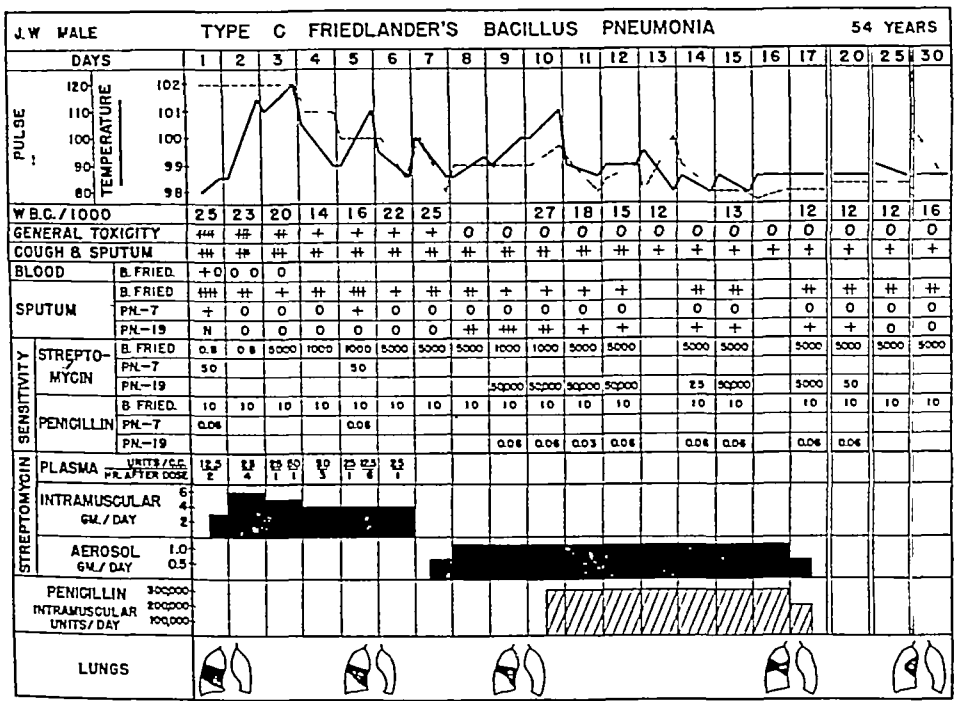


FIGURE 3 Relevant Findings in Case 3

The Friedländer bacillus bacteremia cleared promptly, and the patient improved steadily after streptomycin was started. The bacilli persisted in the sputum and became resistant to streptomycin. Both streptomycin-resistant and streptomycin-sensitive strains of Type 19 pneumococci were obtained, but there was no change in the penicillin-sensitivity of any of the strains.

The Type 19 pneumococcus, although seen earlier in the sputum, was not obtained from the cultures at that time and could not, therefore, be tested for streptomycin sensitivity. When isolated for the first time it was found to be totally resistant to streptomycin, but much more sensitive strains of this type were isolated on two occasions during and after the streptomycin aerosolization. The penicillin sensitivity of all the strains of these three organisms remained unchanged throughout.

Case 4 An 18-year-old single clerk had had a productive cough and suppurative otitis media since the age of 4 and a attack of lobar pneumonia at the age of 14. In January, 1946, he was admitted to the hospital with pneumonia due to a Type 4 pneumococcus of both lower lobes and was treated with penicillin and sulfadiazine. At that time she was found to have serologic evidence of syphilis. She made a seemingly uneventful recovery from the pneumonia and was discharged after 17 days, although cough and expectoration continued and numerous crepitant rales were still heard in both lung bases.

In April the patient was readmitted primarily for further penicillin therapy because of the persistence of positive serologic tests for syphilis. Physical examination revealed no evidence of that disease. There was a moderate amount of

petrous bones, with bilateral obliteration of the mastoid cells. Stained smears of the sputum and of the aural exudate disclosed numerous large encapsulated gram-negative bacilli, and cultures of both showed abundant colonies of Type A Friedländer bacilli.

The patient was given a course of penicillin consisting of 20,000 units intramuscularly every 3 hours for 8 days. At the end of that time there were no changes in the pulmonary or aural findings, and Friedländer bacilli were found repeatedly in cultures of the ear and of the sputum. Cultures of these organisms obtained at different times were completely inhibited by 0.8 or 1.6 units of streptomycin per cubic centimeter. Small numbers of *Staphylococcus albus* inhibited by 12.5 units of streptomycin, were also obtained from cultures of the aural discharge.

Streptomycin therapy was begun on the 12th day in an attempt to influence the infection in the lungs and in the left ear. The relevant data are shown in Figure 4. The dose of streptomycin was 0.5 gm in 2.5 cc of physiologic saline solution intramuscularly every 6 hours and 25 mg (25,000 units) in 1 cc of saline solution instilled into the left auditory canal every 8 hours. The intramuscular injections were discontinued on the 4th day because of severe gluteal tenderness, and inhalations of 0.3 gm in 15 cc. of saline were given instead seven times a day for 9 days.

There was a gradual decrease in the amount of cough and sputum after the streptomycin had been started, and the discharge from the left ear stopped completely after the 3rd day. Sputum cultures continued to yield Friedländer bacilli for 4 days, but the numbers of characteristic colonies of this organism on surface plates declined rapidly during that time and then could not be found in the sputum cultures made after the 1st day of aerosol therapy. The strain isolated on the 4th day was inhibited by 25 units of streptomycin per cubic centimeter, representing a thirty-two-fold increase in resistance over that found before treatment was begun. Colonies of *H. influenzae* were isolated from the sputum for the first time on the 4th day of streptomycin therapy and

anterior chest for which a physician prescribed codeine the day before entry she had chills, fever, increased cough and blood-stained sputum.

On admission the patient was acutely ill and in marked respiratory distress. The respiratory excursions of the left chest were restricted, and there were dullness, diminished tactile fremitus, voice and breath sounds and medium moist rales throughout the left lower lobe. The abdomen showed the uterine enlargement of the third trimester of pregnancy.

The temperature was 102.4°F, the pulse 140, and the respirations 30.

Examination of the blood disclosed a red-cell count of 3,830,000, with a hemoglobin of 63 per cent (Sahli), and a

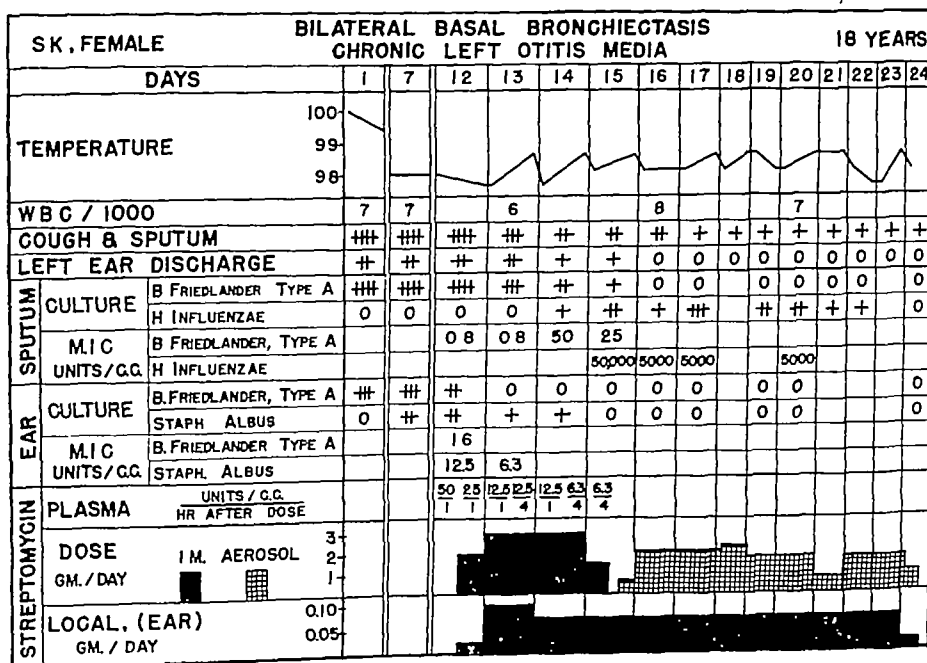


FIGURE 4 Relevant Findings in Case 4

repeatedly thereafter until the last day of that treatment. The organisms required between 5000 and 50,000 units of streptomycin per cubic centimeter for complete inhibition of growth. Cultures of the exudate from the left ear were negative for Friedländer bacilli after the 1st day of streptomycin therapy and for *Staph. albus* after the 3rd day.

The patient was discharged from the hospital after 12 days of streptomycin treatment. At that time the left ear had remained dry, the cough and sputum were markedly decreased, but the auscultatory and roentgenographic signs in the chest were essentially unchanged. Two weeks later she was readmitted to the hospital with lobar pneumonia involving the left lower lobe. A Type 2 pneumococcus was obtained in pure culture from typical rusty sputum. The patient recovered promptly following penicillin therapy. Numerous cultures were negative for both Friedländer bacilli and *H. influenzae* before and during this therapy and during a follow-up period of 2 months. Crepitant rales persisted throughout both lower lobes during this period and roentgenograms continued to show peribronchial thickening.

CASE 5 A 25-year-old married woman in the 7th month of pregnancy, was admitted to the hospital on May 27, 1946. She had had five attacks of pneumonia, a chronic productive cough since the age of 6 and an attack of "pleurisy" in 1945. At the age of 15, she had suddenly had a gross hemoptysis and was studied at another hospital, where a diagnosis of bronchiectasis was made. One week before admission she developed severe and persistent pleuritic pain in the left

white-cell count of 42,700, with 93 per cent neutrophils blood culture was negative. The nonprotein nitrogen was normal. A blood Hinton test and urinalysis were negative. The sputum was mucopurulent and contained no blood and on culture yielded *S. viridans*, *H. influenzae*, *Esch. coli* and occasional colonies of Type A Friedländer bacilli. An x-ray film of the chest showed evidence of some fluid on the left and consolidation in the left lower lobe.

The patient was given oxygen by nasal catheter, morphine initially and then codeine for control of the pleuritic pain and 30,000 units of penicillin intramuscularly every 2 hours. A left thoracentesis, performed on the 2nd day, yielded 150 cc of greenish-yellow, cloudy, malodorous fluid that contained 26,000 pus cells per cubic millimeter. Cultures of the fluid yielded a slowly growing unidentified, gram-negative bacillus. After this thoracentesis 200,000 units of penicillin was injected into the pleural cavity. Another thoracentesis on the 4th day yielded 20 cc of purulent fluid that had no odor and gave no growth. One hundred thousand units of penicillin was injected intrapleurally at that time. Further attempts failed to obtain fluid.

On this regime the patient improved considerably. The temperature, pulse and respiratory rates dropped gradually, and the white-cell count fell to 20,000 but severe cough and profuse expectoration continued. On the 6th day penicillin was given by inhalation as well as intramuscularly, the dose was 25,000 units dissolved in 1 cc of isotonic sodium chloride solution aerosolized every 3 hours. During 1 week of this therapy the patient continued to improve clinically, and

X-ray films of the chest revealed some resolution of the pneumonic process but the severe cough continued and was ill productive of large amounts of greenish purulent sputum. Repeated cultures of the sputum revealed only *H. influenzae* (inhibited by 16 units of streptomycin per cubic centimeter) and *Aerobacter aerogenes* (inhibited by 63 units of streptomycin).

On the 14th day the penicillin by inhalation was discontinued and streptomycin was given by this route in an attempt to diminish the cough and sputum. The dose was 50,000 units in 1 cc of isotonic sodium chloride solution aerosolized five times daily. The administration of 50,000 units of penicillin intramuscularly every 2 hours was continued during the streptomycin inhalation treatment. There was a marked reduction in the cough and sputum within 8 hours after streptomycin was begun and during the last of the 5 days of this therapy it was difficult to obtain sputum for bacteriologic examination. No trace of *H. influenzae* could be found in any of the sputum cultures after the 1st day of streptomycin treatment, *A. aerogenes* likewise disappeared from the sputum for 48 hours but reappeared in small numbers on the 3rd day of treatment. The strain isolated on that day had cultural and biochemical properties identical with those of the pretreatment strains, but it grew in 50,000 units of streptomycin per cubic centimeter. Two subsequent specimens of sputum that the patient was able to produce after therapy also contained small numbers of *A. aerogenes* that were totally resistant to streptomycin.

The streptomycin inhalations were discontinued after 5 days and penicillin aerosolization reinstituted. During the 4th week of hospitalization, the patient had no symptoms, the temperature, pulse and respiration were normal and the white-cell count was 12,000. X-ray films of the chest, however, showed persistence of density in the left lower lobe with marked pleural thickening. On the 29th day the patient left the hospital against advice and subsequent follow-up studies were not possible.

Comment. In this case the relief from the acute pulmonary infection and the probable cure of the putrid empyema must be ascribed largely to the use of penicillin, which was given intramuscularly and by inhalation and, on two occasions, intrapleurally. The pleural exudate, although it yielded a gram-negative bacillus was apparently sterilized on this regime. Streptomycin inhalations were probably responsible for a marked reduction in the cough and expectoration and the rapid elimination of *H. influenzae* from the sputum. *Aerobacter aerogenes*, however, persisted and rapidly became resistant during the streptomycin therapy. The pregnancy was unaffected.

CASE 6. A 44-year-old clerk entered the hospital on December 8, 1945. He had been in excellent health until about 2 years before admission, when he developed a cough that persisted and was productive of yellowish and occasionally blood-streaked sputum. He also began to have moderate dyspnea on exertion. Two weeks before entry he noted an increase in the cough, a reappearance of blood-streaked sputum and some chilliness, fever, malaise and anorexia. High fever, shaking chills and right anterior pleuritic pain began 5 days before admission.

The patient appeared well developed, poorly nourished, anemic and acutely ill. The lips and nail beds were cyanotic. There was moderate clubbing of the fingers. The voice was hoarse, owing to paresis of the left vocal cord. There were typical signs of consolidation of the right lower lobe, and medium crepitant rales and rhonchi were heard over the left lower lobe. The temperature was 102.5°F, the pulse 90 and the respirations 32.

Examination of the blood showed a hemoglobin of 98 per cent (Sahli) and a white-cell count of 16,600, with 84 per cent neutrophils. Blood cultures and urinalysis were negative. Sputum cultures revealed *Staph. albus*, *Micrococcus catarrhalis*, *Streptococcus* and *H. influenzae*. Roentgenograms of the chest showed consolidation of the right lower and middle lobes and patchy areas of density in the left lower lobe.

The antibacterial therapy, the relevant bacteriologic findings and some aspects of the course of the disease over a 20-day period are presented in Figure 5. On admission penicillin was administered by nasal catheter and 20,000 units of penicillin was given intramuscularly every 2 hours. After 10 days the penicillin was discontinued. At that time there

was definite clinical improvement as well as a decrease in the white-cell count and physical signs of resolution in the right lower and middle lobes but the cough continued to be productive of large amounts of purulent sputum.

Three days after the end of penicillin therapy the patient had a shaking chill, the temperature rose to 103°F and all the symptoms recurred. The white-cell count rose to 15,000. A blood culture was negative however and no extension of the pulmonary consolidation could be demonstrated. Sulfadiazine was then given by mouth in a dose of 4 gm followed by 1 gm every 4 hours for 3 days when a generalized scarlatiniform rash appeared. Sulfathiazole in the same dosage was then substituted for the sulfadiazine and penicillin was again given in doses of 20,000 units intramuscularly every 3 hours. The rash was later proved to have been due to barbiturates rather than to sulfadiazine. There was a gradual subsidence of the fever and the acute symptoms and sulfathiazole was omitted after 10 days.

For the next 5 weeks there were no acute symptoms and the temperature remained normal. The patient however lost weight steadily, developed severe night sweats and continued to have severe cough and to produce abundant purulent sputum averaging 150 to 200 cc a day. During that time dietary and vitamin supplements were administered and postural drainage was carried out every 2 hours. Bronchoscopic examination revealed profuse purulent secretions from both lower lobes but no evidence of a tumor stenosis or a foreign body.

During the following 6 weeks the patient was given penicillin by inhalation in doses of 25,000 units at first and later 50,000 units dissolved in 1 cubic centimeter of physiologic saline solution every 3 hours, each dose being preceded by postural drainage. He showed considerable clinical improvement on this regime, his strength and weight increased, and he was able to sit up in a chair and to walk short distances. There was no reduction however in the quantity of sputum raised and x-ray films of the chest revealed marked peribronchial thickening in the right lower lobe and small spotty areas of infiltration throughout the right lower and middle and left lower lobes. These findings were interpreted as indicating advanced bronchiectasis.

During the 15th week the patient suffered a serious relapse. He was seated in a chair when he suddenly became extremely dyspneic and cyanotic and rapidly developed profound shock. Loud gurgling sounds were audible throughout the chest suggesting the presence of acute pulmonary edema but there was no venous distention and an electrocardiogram showed no abnormality except tachycardia. The presence of a ruptured lung abscess appeared likely. The patient was put in a position for postural drainage and 200 cc of yellowish-green malodorous pus immediately drained from the trachea. The foot of the bed was elevated, and he was given oxygen by mask and intramuscular injections of caffeine. Postural drainage was carried out frequently and he was again given 50,000 units of penicillin intramuscularly every 2 hours and sulfadiazine in full doses by mouth. An x-ray film of the chest taken with a portable apparatus showed diffuse haziness and patchy infiltration throughout both lung fields. Cultures of the purulent sputum at that time revealed colonies of *Staph. aureus* and *H. influenzae*, and blood cultures were negative.

The patient remained in a precarious condition for 5 days, but the temperature, pulse and respirations began to drop and the cyanosis lessened. Marked weakness, sweating, anorexia and cough with large amounts of sputum continued. Stained smears of the sputum revealed large numbers of small pleomorphic gram-negative coccobacilli and repeated cultures showed many colonies of *H. influenzae* (sensitive to 16 units of streptomycin per cubic centimeter) with small numbers of *Staph. aureus* colonies (inhibited by 25 units of streptomycin and 7.5 units of penicillin).

Seventeen weeks after admission treatment with streptomycin by inhalation was started with a dose of 250,000 units dissolved in 1.5 cc of physiologic saline solution every 2 hours during the day and every 4 hours at night. Each inhalation was carried out immediately after postural drainage and this therapy was continued for 15 days.

There was no clinical improvement after 5 days of this therapy however and large numbers of *H. influenzae* persisted in smears and cultures of the sputum. After 6 days 1 gm of streptomycin was given intravenously in 20 cc of physiologic saline solution four or five times daily in addition

to the aerosolized streptomycin. It was necessary to administer the intravenous injections at the rate of 1 cc or less a minute, for the patient developed flushing, faintness, headache and vertigo when the drug was given at a faster rate. A total of 33 gm was given intravenously over an 8-day period.

The patient showed no clinical improvement during the 13 days of streptomycin therapy, and he continued to cough up 250 to 500 cc of thick purulent sputum daily. Cultures of the sputum showed a rapid disappearance of the staphylococcus, but *H. influenzae* persisted in almost pure culture. The strain of *H. influenzae* isolated 24 hours after the initial aerosolized dose grew well in the presence of 5000 units of streptomycin per cubic centimeter, and the sensitivity of

the trachea and right main-stem bronchus, with local extension into the mediastinum, chronic pneumonitis of the entire right lung and of the left lower lobe and diffuse bilateral bronchiectasis.

RESULTS

The clinical and bacteriologic results are briefly summarized in Table 1. The first 3 patients received streptomycin for severe pneumonia, which in 2 cases had not responded to treatment with penicillin, supplemented in Case 2 with sulfadiazine.

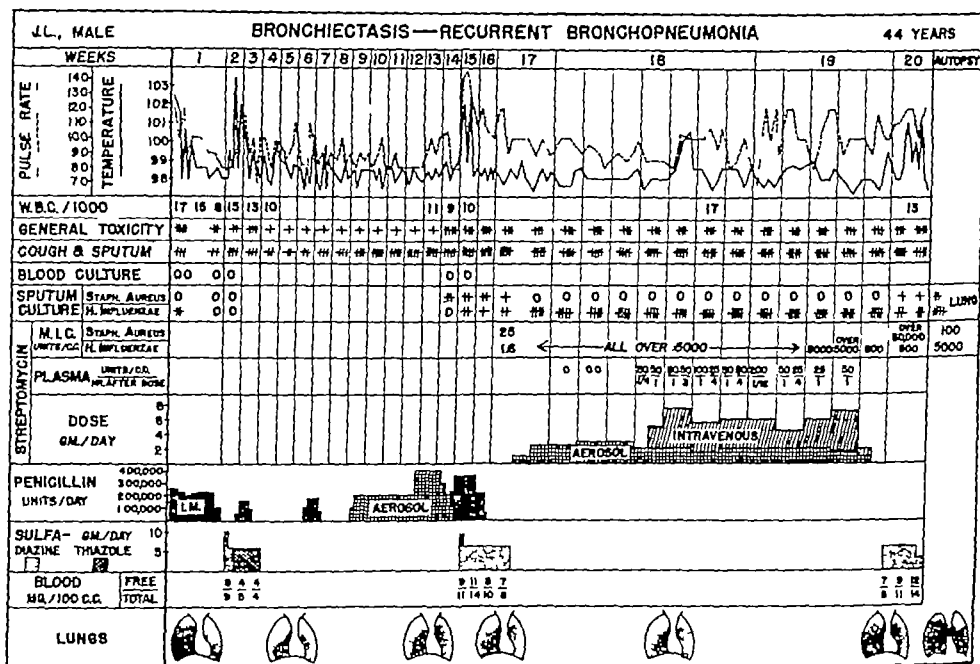


FIGURE 5 Relevant Findings in Case 6

The bronchopulmonary infection was temporarily and only partially improved by sulfonamides and penicillin. Streptomycin therapy was without effect and resulted in the appearance of resistant bacteria in the sputum. Autopsy revealed a bronchogenic carcinoma in addition to extensive pneumonitis and bronchiectasis.

the remaining strains isolated during treatment ranged from 500 to over 5000 units.

Because of the lack of clinical response and the development of fastness by the organism the streptomycin was stopped. Three days later the patient became acutely ill, with fever, increased pulse and respiratory rates and signs of right lower-lobe consolidation. Sputum cultures yielded colonies of *Staph. aureus* that were not inhibited by 50,000 units of streptomycin and of *H. influenzae* that were inhibited by 500 units. Supportive measures and sulfadiazine were given, but the patient became progressively worse and died at the end of the 20th week.

Autopsy. Post-mortem examination revealed reddish-gray consolidation of all lobes except the left upper one. There was extensive dilatation of all bronchi, whose walls were thin but surrounded by fibrotic tissue. Just above the tracheal bifurcation, there was a fleshy, yellowish mass of tumor tissue that had grown through the tracheal wall and extended down the lateral wall of the right main-stem bronchus. The mediastinal lymph nodes were enlarged, firm and filled with carcinomatous tissue. Cultures from the lungs yielded small numbers of *Staph. aureus*, inhibited by 100 units of streptomycin per cubic centimeter, and a heavy growth of *H. influenzae*, inhibited by 5000 units of streptomycin. The final pathological diagnoses were epidermoid carcinoma of

Case 2 ended fatally, but in all 3 cases there was bacteriologic evidence of improvement after streptomycin had been started.

Case 1 was in an aged patient with an extensive pneumonia due to *H. influenzae*. The prognosis at the beginning of streptomycin therapy was considered poor. Rapid clinical improvement followed soon after treatment with streptomycin had been started. The cough and sputum diminished promptly, and the pneumonic process cleared rapidly and then completely. The strain of *H. influenzae* that had been of relatively low susceptibility before treatment rapidly disappeared from the sputum cultures and did not reappear during the follow-up studies.

Case 2 was a pneumonia due to a Type A Friedländer bacillus in which there was no clinical or laboratory evidence of improvement after five days.

intramuscular penicillin, supplemented during the last three and a half days with oral sulfadiazine. The blood culture was negative before and at the end of this therapy. Streptomycin alone was given intramuscularly, and there was definite clinical and bacteriologic improvement. The patient died suddenly on the fourth day of treatment, and autopsy disclosed anatomic findings characteristic of pneumonia due to Friedländer bacillus, with abscess

purulent sputum. The Friedländer bacillus isolated from the sputum on the third day of streptomycin treatment was highly resistant to the action of this drug, and a similar resistance was demonstrated by all the remaining strains of this organism isolated during and after the streptomycin therapy. Shortly after streptomycin had been given by aerosolization, large numbers of Type 19 pneumococci, also highly resistant to streptomycin, were isolated from the

TABLE I. Organisms Isolated from the Sputum or Related to Minimum (Complete) Inhibiting Concentration of Streptomycin

STREPTOMYCIN THERAPY	ORGANISM BEFORE THERAPY	INHIBITING CONCENTRATION OF DRUG	ORGANISM DURING THERAPY	INHIBITING CONCENTRATION OF DRUG	ORGANISM AFTER THERAPY	INHIBITING CONCENTRATION OF DRUG	DEVELOPMENT OF RESISTANCE TO STREPTOMYCIN		CLINICAL RESULT
ROUTE	AMOUNT	units/cc		units/cc		units/cc	INTERNAL	AMOUNT	
	gm						dos	gm	
Intravenous	1.0	<i>H. influenzae</i>	0.0	—	—	—	—	—	Cure
Intramuscular	32.0								
Intravenous	1.0	Type A Friedlander bacillus	0.8	—	—	Type A Friedlander bacillus*	0.8	—	Death
Intramuscular	14.0								
Intramuscular	26.0	Type C Friedlander bacillus	0.8	Type C Friedlander bacillus	1,000–1,000	Type C Friedlander bacillus	0.00	2	10.0
									Recovery with abscess formation
Intramuscular	12.5	Type 7 pneumococcus	0.0	Type 7 pneumococcus	50	—	—	—	
		Type 19 pneumococcus	—	Type 19 pneumococcus	2.0–50,000	Type 19 pneumococcus	0	8	26.0
Intramuscular	8.5	Type A Friedlander bacillus	0.8	Type A Friedlander bacillus	25–0	<i>S. typhimurium</i>	—	2	6.0
Intramuscular	16.0			<i>H. influenzae</i>	1,000–10,000				Decreased cough and sputum lung signs unchanged
Intramuscular	7.5	<i>A. aerogenes</i>	6.3	<i>A. aerogenes</i>	> 0.000	<i>A. aerogenes</i>	> 0.000	4.5	Decreased cough and sputum lung signs unchanged
		<i>H. influenzae</i>	1.6						
Intramuscular	27.0	<i>H. influenzae</i>	1.6	<i>H. influenzae</i>	50,000	<i>H. influenzae</i>	0.0–0.000	1	2.0
									Temporary improvement
Intramuscular	10.0	<i>Staph. aureus</i>	25.0			<i>Staph. aureus</i>	> 0.000	1	10.0
									Death bronchogenic carcinoma found at autopsy

* For a full description of lung at autopsy. The pretreatment culture of the sputum showed Type A Friedländer bacilli. A minimum inhibiting concentration of 1.6 units per cubic centimeter and *Staph. aureus* with a minimum inhibiting concentration of 12.5 units per cubic centimeter. A strain of the *Staph. aureus* with a minimum inhibiting concentration of 6.25 units per cubic centimeter was obtained on the second

in most of the right upper and middle lobes. Although Friedländer bacilli could not be obtained from the sputum during the last two days of therapy, they were recovered from the lungs at autopsy, and were then found to be as sensitive to streptomycin as the pretreatment strains. Case 3 was one of severe pneumonia due to a Type C Friedländer bacillus with bacteremia. The patient was in a shock-like state and almost moribund at the time of admission. Antibacterial therapy during the early acute stage was limited to intramuscular streptomycin. This produced a prompt clearing of the bacteremia and marked clinical improvement. The pulmonary infection, however, instead of clearing completely, became chronic, and definite abscesses formed. Although the patient was afebrile and free of systemic symptoms for three months after treatment, he continued to cough and to produce large amounts of

sputum. After seven days of treatment with intramuscular penicillin, the numbers of pneumococci diminished markedly, although a few colonies of these organisms and many colonies of Friedländer bacilli were repeatedly found in the sputum cultures made during and after the course of penicillin. It is of interest that, whereas both the gram-positive and the gram-negative organisms became markedly resistant to streptomycin during treatment with this antibiotic, neither strain showed any change in sensitivity to penicillin during or after administration of that agent.

The 3 remaining cases represent chronic and recurrent bronchopulmonary infections in which gram-negative bacilli were found in large numbers in the sputum. The streptomycin was used in these cases in an attempt to reduce the amount of cough and sputum by inhibiting or eliminating the gram-negative flora. Each of these patients had received

a fairly long course of penicillin intramuscularly, and 2 of them had also received that antibiotic by inhalation with only partial or temporary relief before streptomycin treatment was started.

In Cases 4 and 5 definite clinical improvement occurred after the streptomycin had been begun. The cough was markedly reduced, and the small amounts of sputum that the patients continued to raise appeared clear rather than purulent. In Case 4, except during the brief attack of Type 2 pneumococcus pneumonia of the left lower lobe that occurred two weeks after streptomycin treatment, the lung findings were essentially unchanged for three months. In this case a thirty-two-fold increase in streptomycin resistance was demonstrated by the Friedländer bacillus, and a strain of *H. influenzae* isolated during treatment was highly resistant to the action of that drug. Neither of these organisms, however, was recovered from sputum cultures during a three-month period after streptomycin treatment.

Of particular interest in Case 4 was the rapid clearing of the purulent discharge from the left ear following the intramuscular and topical streptomycin therapy. Many different types of local and systemic therapy, including long courses of penicillin and sulfonamides, had previously failed to accomplish this result. The ear remained dry and the cultures free of Friedländer bacilli throughout the follow-up period.

Adequate follow-up studies were not conducted in Case 5, but the lung findings were also essentially unchanged ten days after the conclusion of streptomycin therapy. Small numbers of a resistant strain of *A. aerogenes* were recovered from sputum cultures both during and after treatment.

In Case 6 there was no improvement in spite of large doses of streptomycin intravenously and by inhalation, and the patient died soon after this therapy was concluded. *H. influenzae*, the predominant organism in sputum cultures, persisted throughout the period of therapy. There was a marked increase in streptomycin-resistance of this organism within twenty-four hours of treatment. In this case the chronic pulmonary infection was associated with a bronchogenic carcinoma whose diagnosis had been suspected during life but was definitely established only at autopsy.

Untoward Reactions

These were infrequent and minimal. Pain and tenderness in the region of the intramuscular injections were noted in every case, and in Case 4 the sites became red and indurated. Increasing fever during the latter part of the course of streptomycin in Case 1 was probably due to streptomycin, since the temperature dropped steadily after the antibiotic was discontinued. In Case 6 the intravenous injections were accompanied by faintness, flushing and headache when the solution was given at too

rapid a rate. There were no untoward reactions to the nebulized streptomycin in any of the patients. Disorders of labyrinthine or eighth-nerve function were not observed in these cases.

Streptomycin Levels

In all the patients who received streptomycin by the intravenous or intramuscular route, the levels of streptomycin in the plasma measured at various intervals following individual injections throughout therapy were, for the most part, equal to or higher than the in vitro sensitivity of the infecting organism that had been obtained before treatment. The levels corresponded, in general, to those obtained in other patients receiving similar doses of streptomycin. Progressive increases in streptomycin level in the blood were not observed. Blood obtained from 3 patients during and at short intervals after the aerosolization of streptomycin, when they were not receiving systemic therapy, failed to show detectable amounts of the antibiotic.

DISCUSSION

It is not possible to draw final conclusions regarding the value of streptomycin in pulmonary infections, because relatively few cases have been treated. The clinical results, however, in this small series of cases and in those reported in the literature indicate that some patients with pneumonia and certain others with recurrent or chronic bronchopulmonary infections caused by gram-negative bacilli respond favorably to streptomycin therapy. In some cases this drug seems to be life-saving. There are other patients, however, who seem to derive little or no benefit from large doses of streptomycin and in whom the infection may become or remain chronic or may terminate fatally. In certain cases the poor results may be associated with the rapid development of streptomycin fastness by the infecting organisms.

The recovery of streptomycin-resistant bacterial strains during and after treatment in patients with urinary-tract infections,^{14, 16-18} meningitis,^{6, 7, 19} tuberculosis,²⁰ osteomyelitis²¹ and ozena⁹ has been reported, but the same phenomenon has not been described in pulmonary infections due to gram-negative bacilli. Ten separate bacterial strains were isolated from the sputum of these 6 patients before streptomycin treatment was begun, and a significant increase in resistance to streptomycin occurred in 5 during or after the course of therapy. Nine strains of organisms not isolated before therapy were first obtained from cultures of the sputum during the course of streptomycin treatment in 2 cases. Both strains were also highly resistant to the action of the drug. The appearance of resistant bacteria during therapy may be an important factor in determining the eventual clinical results. In Case 6 streptomycin resistance developed rapidly and there was no beneficial effect from the treatment.

Case 3 there was a good clinical response initially, but a streptomycin-fast strain developed and the pulmonary infection became chronic.

The development of drug fastness by the infecting organisms, however, is not the sole factor in determining the clinical result. In 2 cases of bronchiectasis and in a severe case of pneumonia due to Friedländer bacillus there was marked symptomatic improvement despite the appearance of streptomycin-fast strains in sputum cultures. A third patient died of pneumonia caused by Friedländer bacillus during the course of therapy and the strain recovered from the lung at autopsy was identical in its streptomycin sensitivity with the one obtained before treatment.

The basic conditions that give rise to the development of resistance are virtually unknown and it becomes difficult to understand why certain cases show the development of resistant strains and others do not. Two of these cases (Cases 2 and 3) were clinically and bacteriologically similar and both had acute pulmonary infections that appeared to be similar in location and extent, the strains of Friedländer bacillus isolated in each case before treatment showed identical sensitivities to streptomycin by the method used, and the doses of streptomycin were comparable. Nevertheless, the Friedländer bacillus in Case 3 became streptomycin resistant, whereas a similar organism in Case 2 retained its original sensitivity.

Another point worth mentioning is the wide differences in sensitivity of strains of the same organisms isolated at different times after resistance had developed. This suggests that organisms of different resistance coexist in the same exudate and that, since single-colony cultures are tested, the sensitivity of the particular strain tested may be only a matter of chance.

It has been suggested that the maintenance of an alkaline reaction during treatment of urinary-tract infections enhances the antibiotic activity of streptomycin and thereby prevents or curtails the development of bacterial resistance.^{14, 18} Offhand, it does not seem feasible to maintain an alkaline reaction in the infected tissues and exudate in pulmonary infections.

The mortality rate in pulmonary infections due to gram-negative bacilli is high even with the best forms of therapy. Bronchiectasis caused by gram-negative bacilli is often progressive and refractory to the usual antibiotic and chemotherapeutic treatment, and is not always amenable to surgery. Prolonged courses of sulfonamides and penicillin are helpful in some cases. Streptomycin, however, appears at present to be the therapy of choice in such cases, although as in the streptomycin treatment of other infections, clinical failures may result. Obviously, it cannot be expected that the structural damage in chronic cases will be repaired, but healing

may be promoted by the reduction in or the elimination of the infection in such cases. In patients with abscesses or with large bronchiectatic cavities streptomycin by inhalation preceded each time by postural drainage may be the method of choice when susceptible gram-negative bacilli are present in abundance. The inhalations should probably be supplemented by systemic therapy, particularly if there is an accompanying acute pneumonitis.

The favorable results in cases of pulmonary and meningeal infections with *H. influenzae* suggest a possible use of streptomycin in certain severe epidemics of virus influenza in which pulmonary infections are associated with that organism. There is reason to believe that most of the fatal pulmonary complications of epidemic influenza are due not to the virus alone but to its association with hemolytic streptococci, staphylococci, pneumococci and influenza bacilli. Penicillin and sulfonamides should prove effective in cases in which gram-positive cocci are involved, and streptomycin may fill the gap in those due to *H. influenzae*, which is only slightly — if at all — affected by the other agents.

SUMMARY

Three cases of acute and 3 of chronic pulmonary infections caused by gram-negative bacilli are presented, and the clinical and bacteriologic results of treatment with streptomycin outlined. The results of therapy were favorable, although not uniformly so. One of the causes of clinical failure appears to be the rapid development of streptomycin resistance by the infecting organisms. In 1 case drainage from a chronic suppurative otitis media stopped promptly after systemic and local streptomycin therapy.

REFERENCES

1. Schatz A, Bugie E and Waksman S A. Streptomycin substance exhibiting antibiotic activity against gram positive and gram-negative bacteria. *Proc Soc Exper Biol & Med* 55:66-69 1944
2. Heilman F R. Streptomycin in treatment of experimental infections with micro-organisms of Friedländer group (Klebsiella). *Proc Staff Meet Mayo Clin* 20:33-39 1945
3. Waksman S A and Schatz A. Streptomycin — origin, nature and properties. *J Am Pharm Assoc (Scient Ed)* 34:273-291 1945
4. Hegarty C P, Thiele E and Verwey W F. In vitro and in vivo activity of streptomycin against *Hemophilus pertussis*. *J Bact* 50:651-654 1945
5. Hewitt W L and Pittman M. Antibacterial action of penicillin, penicillin N, and streptomycin on *Hemophilus influenzae*. *Pub Health Rep* 61:768-778 1946
6. Birmingham J R, Kave R and Smith M H D. Streptomycin in treatment of influenza meningitis. *J Pediatr* 29:113 1946
7. Alexander H E and Leidy G. Influence of streptomycin on Type B *Hemophilus influenzae*. *Science* 104:101 1946
8. Herrell W E and Nichols D E. Clinical use of streptomycin: study of forty-five cases. *Proc Staff Meet Mayo Clin* 20:449-462 1945
9. Olsen A M. Streptomycin aerosol in treatment of chronic bronchiectasis: preliminary report. *Proc Staff Meet Mayo Clin* 21:5 1946
10. Durant T M, Sokalechuk A J, Norris C M and Brown C L. Streptomycin therapy in *Hemophilus influenzae* pulmonary infections. *J A M A* 131:194-196 1946
11. Learner N and Minnich W R. Friedländer pneumonia treated with streptomycin: report of case with prompt recovery. *Ann Int Med* 25:516-525 1946
12. Bishop C A and Rasmussen R F. Klebsiella pneumonia treated with streptomycin. *J A M A* 131:821 1946
13. Committee on Chemotherapeutics and Other Agents. National Research Council. Streptomycin in treatment of infections: report of one thousand cases. *J A M A* 132:411 and 70-77 1946

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TABLE 1 Sensitivity to 1 in 100 Substances as Demonstrated by Skin Tests

Case No.	LIVER EXTRACT*				CHOLESTEROL EXTRACT*				ALL PROTEIN MUSCULAR EXTRACT				TAXM modified	TAXM unmodified
	1:10000	1:1000	1:100	1:10	1:10000	1:1000	1:100	1:10	1:10000	1:1000	1:100	1:10	1:10000	1:1000
1	++	++	++	++	0	0	0	0	0	0	0	0	0	0
2	++	++	++	++	0	0	0	0	0	0	0	0	0	0
3	++	++	++	++	0	0	0	0	0	0	0	0	0	0
4	++	++	++	++	0	0	0	0	0	0	0	0	0	0
5	++	++	++	++	0	0	0	0	0	0	0	0	0	0
6	++	++	++	++	0	0	0	0	0	0	0	0	0	0
7	++	++	++	++	0	0	0	0	0	0	0	0	0	0
10	++	++	++	++	0	0	0	0	0	0	0	0	0	0
11	++	++	++	++	0	0	0	0	0	0	0	0	0	0
13	++	++	++	++	0	0	0	0	0	0	0	0	0	0

*15 U S P units per cubic centimeter
† 2 U S P units per cubic centimeter

TABLE 2 Clinical Data in 14 Patients Sensitive to Liver Extract

Case No	Age	Race	Sex	Diagnosis	Dosage of Pork Liver Extract*	Injection before First Reaction	No of Reactions	Clinical Signs of Sensitivity	Dosage of Beef Liver Extract*	Frequency of Treatment	Remarks
1	60	W	F	Pernicious anemia	1 (monthly)	13	2	Collapse, vomiting, cyanosis and thready pulse	1 (monthly)	8 injections in 9 mo	Beef liver extract first given in small doses as a test
2	60	W	F	Pernicious anemia	1 (monthly)	4	1	Collapse, itching, nausea and vomiting	1 (monthly)	13 injections in 1 yr	Sensitivity to beef liver manifested after thirteenth and fourteenth injections
3	59	W	F	Pernicious anemia	1 (monthly)	7	4	Urticaria, itching and edema of lips	1 (monthly)	24 injections in 2 1/2 yr	Itching of palms after eighth injection of beef liver followed by desensitization and no further difficulty
4	32	W	F	Sprue	1 (monthly)	Many	Many	Edema and itching at site of injection	1 (twice monthly)	24 injections in 1 yr	Initial desensitization to beef liver with out difficulty
5	41	W	F	Pernicious anemia	1 (monthly)	4	6	Nausea and vomiting	1 (monthly)	13 injections in 1 yr	
6	41	W	F	Pernicious anemia	1 (monthly)	Many†	Many	Nausea, vomiting general itching and site of injection	1 (twice weekly)	5 injections weekly	
7	68	W	F	Pernicious anemia	1 (monthly)	18	5	Flushing of face nausea and urticaria	1 (monthly)	5 injections in 5 mo	
8	53	W	F	Pernicious anemia	1 (monthly)	14	2	Flushing of face, itching and edema of lips	1 (monthly)	12 injections in 1 yr	
9	57	W	F	Pernicious anemia	1 (monthly)	18	3	Urticaria, itching and edema of lips	1 (monthly)	20 injections in 1 yr	
10	69	W	F	Pernicious anemia	1 (monthly)	12	1	Urticaria, itching and edema of lips	1 (monthly)	2 injections in 2 yr	
11	34	N	F	Pernicious anemia	1 (monthly)	6	2	Urticaria and itching	1 (monthly)	17 injections in 2 1/2 yr	Itching after tenth injection of beef liver, followed by desensitization without further difficulty
12	78	W	M	Pernicious anemia	1 (monthly)	7	16	Edema of lips, followed by nausea and collapse	1 (monthly)	17 injections in 1 1/2 yr	
13	55	W	F	Pernicious anemia	Irregular	10	10	Urticaria, itching and edema of face	1 (four times weekly)	13 injections in 1 yr	
14	55	W	F	Pernicious anemia	Irregular	18	2	Collapse, nausea, headache and asthma	1 (twice weekly)	Four injections in 2 wk	

*15 U S P units per cubic centimeter
†14 received injections for more than four years

- 14 Finland, M, Murray R., Harris H W, Kilham, L., and Meads, M Development of streptomycin resistance during treatment. *J A M A* 132 16-21, 1946
- 15 Barach A L Silberstein, F H, Oppenheimer, E T, Hunter T and Soroka M Inhalation of penicillin aerosol in patients with bronchial asthma chronic bronchitis, bronchiectasis and lung abscess preliminary report *Ann Int Med* 22 485 509 1945
- 16 Petroff, B P and Lucas, F V Streptomycin in urinary infections *Ann Surg* 123 808-818 1946
- 17 Bondi, A, Jr, Ottenberg D, Dietz, C C, and Brown C L Streptomycin therapy in infection of urinary tract failure because of development of resistance *J A M A* 132 634, 1946
- 18 Harris H W, Murray R., Paine, T F Kilham, L., and Finland M Streptomycin treatment of urinary tract infections with special reference to use of alkali *Am J Med* 2 229-250, 1947
- 19 Alexander, H E, Leidy, G Rake G, and Donovan, R Hemophilus influenzae meningitis treated with streptomycin *J A M A* 132, 434-440, 1946
- 20 Youmans, G P, Williston E H, Feldman W H., and Hissaw, H W Increase in resistance of tubercle bacilli to streptomycin preliminary report *Proc Staff Meet, Mayo Clin* 21 126 1946
- 21 Edwards, M W, and Kirk, G D Development of resistance to streptomycin by *Aerobacter cloacae* *Am J Clin Path* 16 527 529 1946

SENSITIVITY TO PORK-LIVER EXTRACT IN PERNICIOUS ANEMIA*

Clinical Observations on Fourteen Patients

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NOT until several years after the classic report of Minot and Murphy¹ on the treatment of pernicious anemia with liver was a potent injectable liver extract first employed for the routine therapy of this disease. In 1933 Gänsslen² gave scant details of the method of preparation but described striking hematologic and clinical effects with the product later well known under the proprietary name of "Campolon." Subsequently, the cases of at least 175 patients who were sensitive to liver extract have been reported, half of them in the last three years. Individual studies indicate that such sensitivity is not a rare condition. Delikat³ reported 14 cases, Feinberg, Alt and Young⁴ recently reported 8 cases, McSorley and Davidson⁵ encountered 40 cases in the past ten years, Kaufman, Farmer and Reich⁶ reviewed 11 cases and Schwartz and Legere⁷ observed 68 cases in 396 outpatients. In view of the number of recent reports, it is apparent that sensitivity is an important complication in patients receiving liver-extract therapy.

This report is based on 14 patients discovered in the past two and a half years to be sensitive to injections of liver extract. The total number of patients under observation during this period was about 200. The clinical manifestations of sensitivity exhibited by the patients can be divided into three varieties. The most frequent effect consisted of generalized itching, urticaria, edema of the face and lips, nausea and vomiting. The second type exhibited peripheral vascular collapse, including thready pulse, sweating, cyanosis, weakness and fainting. A third group of patients manifested local

signs that may have been due to an Arthus type o sensitivity consisting of swelling, itching and in duration without necrosis at the site of injection. Only one patient suffered from asthma. In all cases the immediate symptoms were relieved, at least in part, by the injection of adrenalin.

The maintenance of adequate parenteral therapy with liver extract in sensitive patients may be a difficult problem. In the cases discussed below subsequent reactions were prevented by the employment of an injectable liver extract prepared from another animal source. This success occurred in many cases without complete correlation with the sensitivity as demonstrated by skin tests.

MATERIALS AND METHODS

The purified liver extract containing 15 U S P units per cubic centimeter that had been routinely used in the treatment of patients who had become sensitized was prepared from pork liver, as are apparently, the majority of liver extracts on the market at present. The injectable liver extract employed for testing for sensitivity and administered subsequently by intramuscular injection were prepared from pork, beef and lamb and were of two potencies crude (2 U S P units per cubic centimeter) and purified (15 U S P units per cubic centimeter).¶ For skin testing the extracts were diluted under sterile conditions with physiologic saline solution in the proportions of 1:100 and 1:1000. The special muscle extracts used for skin testing were made from pork, beef and lamb muscle. They were employed undiluted and also diluted with physiologic saline solution in a proportion of 1:10.

All skin tests were performed after the patient had developed sensitivity to pork-liver extract and during the course of therapy with beef-liver extract. They were done by the intracutaneous injection of

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tively weak reactions obtained with muscle extracts, we believe that no confirmatory evidence of species specificity can be derived from them.

There is a difference of opinion in the literature regarding the cause and nature of the sensitivity to intramuscular liver extract. In contrast to our experience, most authors favor Cnep's⁸ impression that the sensitivity is primarily of organ specificity, and all agree that it represents an acquired type of sensitivity. Cnep based his conclusions on the fact that he obtained positive skin tests with liver extracts derived from hog, beef, sheep and chicken and negative tests when muscle extracts from the same animals were used. He believed that the sensitivity was to the liver proteins themselves. Andrews⁹ suggested that the allergenic factor was the antianemic principle itself and that changing the animal source of the extract would not eliminate sensitivity reactions. Kaufman, Farmer and Reich⁶ reported observations on 11 sensitive patients in whom the skin tests indicated that the sensitivity was to the organ and not to the animal. Feinberg, Alt and Young⁴ concluded, in the 8 cases that they studied, that the sensitivity was to a special organ fraction associated with the antianemic factor. They reported a patient, however, who was able to tolerate intramuscular injections of beef-liver extract but not of extract derived from pork liver. Engelhardt and Derbes¹⁰ suggested that reactions in some cases were due to impurities but that in general the sensitivity was to the organ and not to the animal from which the extract had been prepared.

On the other hand, there is evidence in the literature to support our conclusion that biologic specificity is a significant — if not the most important — factor in sensitivity to liver extract. Rynes and Tocantins,¹¹ in an excellent review of the literature on sensitivity to liver extract, presented the case of a patient who was able to tolerate beef liver extract but when given pork-liver extract exhibited an Arthus type of sensitivity. Nausea was induced when this patient was given pork to eat. Skin tests, however, were positive for liver and muscle extracts of pork, beef and lamb. The authors concluded that the cases represented a biologic type of sensitivity. In 2 cases reported by Jones¹² 1 patient tolerated without difficulty intramuscular injections of liver extract prepared from beef but reacted severely to an extract of pork origin. Skin tests, however, as in our Case 2, indicated that the patient was sensitive to both liver extracts. Later, the patient was given a horse-liver extract without difficulty. In a patient reported by Bynum,¹³ sensitivity first ap-

peared after eleven injections of an extract, Reticulogen (Lilly), stated to be prepared from pork. The patient tolerated without difficulty injections of an extract derived from beef liver.

Most authors who explain liver-extract sensitivity by organ specificity base their conclusions on the results of skin tests with liver and muscle extracts. From an analysis of the cases included in this report, it is evident that the change in therapy to an extract from a different animal source resulted in the abolition of sensitivity symptoms regardless of the results of the skin tests. Sensitization to liver extracts derived from pork rather than from beef liver predominates in all probability because most of the commercial extracts used in this country are derived from pork liver. Certainly some persons may have an organ-specific sensitivity but no such cases were encountered in our series.

SUMMARY

Fourteen cases of acquired sensitivity to a pork-liver extract given intramuscularly are reported. Symptoms of sensitivity were abolished by a change of the therapy to an extract derived from beef liver.

Skin tests with liver extracts derived from pork, beef and lamb indicated in general greater sensitivity to extract of pork liver than to that of beef and lamb liver.

In the cases studied, clinical experience consistently — and skin tests to some extent — indicated that the sensitivity to liver extract represented an acquired type of species rather than one of organ specificity.

REFERENCES

1. Mino, G. R. and Murphy, W. P. Treatment of pernicious anemia by special diet. *J. A. M. A.* 87:470-476, 1926.
2. Gänsslen, M. Die Lebertherapie. *Fortschr. d. Med.* 51:615-625, 1935.
3. Delikat, E. Intolerance to liver extract in pernicious anaemia. *Brit. M. J.* 1:559, 1944.
4. Feinberg, S. M., Alt, H. L. and Young, R. H. Allergy to injectable liver extracts: clinical and immunological observations. *Ann. Int. Med.* 18:511-522, 1944.
5. McSorley, J. G., and Davidson, L. S. P. Sensitivity to liver extract. *Bru. M. J.* 1:714-716, 1944.
6. Kaufman, R. E., Farmer, L. and Reich, C. Allergic reactions to liver extract. *Ann. Int. Med.* 19:768-779, 1943.
7. Schwartz, S. O. and Legere, H. Treatment of liver extract sensitivity. *Blood* 1:507-516, 1946.
8. Cnep, L. H. Allergy to liver extract. *J. A. M. A.* 110:66-68, 1935.
9. Andrews, C. T. Allergic reaction to liver extract. *Lancet* 1:664, 1941.
10. Engelhardt, H. T. and Derbes, V. J. Allergy to liver extract. *South. M. J.* 37:51-54, 1944.
11. Rynes, S. E. and Tocantins, L. M. Arthus type of sensitivity to liver extract. *J. Allergy* 15:175-181, 1944.
12. Jones, C. A. Allergic reactions following parenteral administration of liver extract. *Internat. Clin.* 3:258-263, 1959.
13. Bynum, W. T. Allergy to liver extract. *J. Oklahoma M. A.* 34:55-57, 1941.

from 0.01 to 0.02 cc of the preparations mentioned above. Sterile physiologic saline solution was used as the control. Nearly all the skin tests were made by the same person and were read at intervals of five, ten, twenty and thirty minutes. The tests were interpreted as follows: 0 = negative (same as control), + = small regular wheal with slight erythema, ++ = moderate-sized wheal (up to 10 mm in diameter) with definite erythema, +++ = irregular wheal over 10 mm in diameter, without definite pseudopods but with definite erythema, and ++++ = large wheal with definite pseudopods and erythema. The results of the tests are presented in Table 1. The symbols given in the table represent the maximum reaction noted. Most authors agree that the presence of pseudopods constitutes a definitely positive skin test. On the basis of our criteria, however, both +++ and ++++ reactions were considered indicative of sensitivity.

RESULTS

After four to eighteen or more monthly intramuscular injections, the 14 patients became sensitive to the purified extract containing 15 USP units per cubic centimeter and prepared from pork liver. The clinical information in these cases is summarized in Table 2.

None of the patients who became sensitive to liver extract prepared from pork experienced distressing symptoms when given an extract derived from beef liver. This change was made after reactions had occurred on one to eighteen occasions, or more, following the intramuscular administration of the commercial pork-liver extract. In 11 of the 14 cases (Cases 1, 4-10 and 12-14) this change in therapy completely — and so far, permanently — abolished all signs or symptoms of sensitivity. In Cases 3 and 11, however, after the eighth and tenth monthly injections of the beef-liver extract, respectively, itching of the palms occurred. Thereupon, both patients were desensitized by initially small (0.1 cc) and gradually increasing (up to 1.0 cc) weekly injections of the beef-liver extract. No further reactions occurred with subsequent monthly injections. Following the thirteenth injection, the patient in Case 2 experienced itching of the palms. She was apprehensive concerning another severe reaction and for this reason refused further injections. Consequently, desensitization was not possible. She is now being successfully treated with an orally administered liver extract prepared from pork. Two of the patients sensitive to pork-liver extract were given beef-liver extract initially in small doses, with an increase at weekly intervals to 1 cc. This was done as a further precaution, since the reactions to the pork-liver extract had been extremely severe.

The patient in Case 10, having been found sensitive to pork-liver extract and having been shifted to beef-liver extract, was subsequently given by

error an injection of 1 cc of a liver extract derived from pork. This was immediately followed by a severe reaction characterized by generalized itching, nausea, vomiting, feeble pulse and weakness. Treatment with beef-liver extract was subsequently resumed without difficulty.

The patients sensitive to liver extract prepared from pork who were skin tested, with one possible exception, exhibited greater sensitivity by this procedure to pork-liver extract than to extracts of beef or lamb liver (Table 1). The few skin tests with allergenic muscle extracts prepared from the same animal sources were negative or only questionably positive in most cases. In Case 6, although the patient was sensitive to pork-liver extract clinically and on the basis of skin tests, reactions with pork-muscle extracts were negative and those with lamb-muscle extracts were positive. In the other patients tested with the muscle extracts a greater sensitivity to pork muscle was observed.

It is difficult to correlate the clinical severity of the reactions with the results of the skin tests. Case 1 provided the most striking example of this discrepancy. In spite of severe reactions clinically, skin tests with pork-liver extract showed only moderately positive reactions. Only 1 patient (Case 6) gave a history of other allergic tendencies. She stated that she was unable to tolerate aspirin, codeine or barbiturates. She gave no history of asthma or hay fever.

As pointed out by many other investigators, the duration of therapy before symptoms of sensitivity appear varies tremendously. In the present series initial symptoms of sensitivity developed earliest after the fourth injection and at the latest after eighteen or possibly more injections over a period of years. The duration and the amount of treatment before the onset of reactions had no apparent relation to the severity of the symptoms.

Thirteen of the 14 patients included in this report were women. The frequency of liver-extract sensitivity among women has been observed by others. Kaufman, Farmer and Reich⁶ reported that 70 per cent of all recorded cases had occurred in females.

DISCUSSION

In treating patients with pernicious anemia who became sensitive to pork-liver extract, we were usually able to eliminate manifestations of sensitivity by changing the therapy to an extract derived from beef liver presumably by about the same method. This suggested that the sensitivity was of species-specific rather than organ-specific type, since the patients would otherwise have suffered further reactions when beef-liver extract was substituted for that derived from pork liver. The results of the skin tests in general confirmed this hypothesis. The majority of the patients showed a greater sensitivity to extracts of pork liver than to those of beef or lamb liver. Because of the rela-

often be cured, or at least arrested, if treated in time

The Commonwealth has assumed responsibility for the care of cases of communicable disease for over half a century. Automatically, as soon as the Department of Public Health declares a disease to be dangerous to the public health, the local board of health becomes responsible for the care of the patient, provided he is unable to pay for treatment himself. If the patient with a communicable disease is a state settled case, he becomes the responsibility of the Department of Public Welfare. The local boards of health and of welfare have been giving medical care on the local level for many years.

The Department of Public Health also furnishes treatment for cases of venereal disease. It maintains twenty-five clinics, which co-operate with the local hospitals. Moreover, free transportation is furnished, if necessary. It provides specific drugs, including the sulfonamides, free of charge to private practitioners for the treatment of venereal diseases, but the physician must be remunerated by the patient for the services he renders, penicillin is furnished without cost to the Co-operating Venereal Disease Clinics.

Another series of clinics that the Department of Public Health sponsors are those for crippled children. These clinics care for any child whose family cannot afford the expensive and long-continued medical treatment necessitated by his crippled condition. All such cases are referred by the family physician or some social agency. A new project is now under way for the care of patients with rheumatic fever. Facilities that have been made available at the North Reading State Sanatorium will make it possible to proceed as soon as adequate personnel is available.

The Commonwealth has been reasonably successful in controlling infectious diseases. In the days of Paul Revere the normal life expectancy was thirty-five years. Today it is sixty-five, and in the near future it will probably be extended to seventy-five. Not much has been accomplished, however, in the care of the chronically ill. Plans are being drawn up for a new chronic-disease hospital at Stoneham, which will accept three types of patients: those in need of hospitalization, those whose treatment will contribute to knowledge of the disease and of methods for diagnosis and treatment, and those with cases that will furnish instruction for doctors and students in the various aspects of the disease. This will not be a custodial institution, but every effort will be made to get the patient on his feet so that he may be discharged. There will also be a large outpatient clinic. Patients will be admitted to this hospital under the same conditions as those governing the admission of cancer patients, few of whom pay any part of their expenses.

* * *

Public health has made outstanding progress in the prevention of disease, and in the phases of medi-

cal care mentioned above. In spite of the fact, however, that well administered health departments are an accepted part of state government, approximately a third of the nation's population are actually living in communities not covered by public health services. Thus, many citizens of the Commonwealth are deprived of the benefits of the latest developments of medical science and preventive medicine. One of the major problems in Massachusetts is the establishment of adequate local health facilities for all the people. Only by the provision of such facilities under the direction of a full-time, trained and experienced health officer can the citizens of any area attain the greatest benefits from sanitation, prevention of communicable diseases, adequate nutrition and all the other factors that ultimately, in their full utilization, bring about the achievement of optimal health. The national welfare demands that the people in small towns receive the same benefits as those in large cities.

Perhaps a definition of the term "optimal health" should be given. If a person is enabled to develop his physical and mental health to the highest degree and to maintain them at high level, he has achieved optimal health — in other words, he is given the opportunity to develop and to utilize the potentials with which Nature has endowed him so as to obtain satisfaction from life and to contribute the greatest effort to the community. Optimal health, therefore, is the summation of the achievements in all spheres of the medical sciences and the healing arts that bring about the greatest happiness, the greatest utilization of one's abilities, the longest life span and the greatest good to the individual, his family and his community.

The responsibility for making available these benefits of medical science and the healing arts rests first with the family, secondly with the official community agencies and thirdly with the voluntary agencies. The health of a person is essentially his responsibility — only if he neglects his health or if his illness adversely affects the community in which he lives does he become a problem of the community. Leaders in the field of public health believe in the rights of individuals. They believe that medical care is a man's own responsibility, just as his family is his responsibility, he should provide such care if he able to do so. Neglect of his health may be due to carelessness and to lack of consideration for his family and his neighbors or to inability to obtain adequate means of prevention or of treatment. Whenever an illness affects other members of the community, health is no longer a purely personal problem but becomes the responsibility of the community as well. The provision of medical care for a patient who has scarlet fever is a family obligation, but his isolation and the quarantine of his contacts are the responsibility of the community. If the family is unable to provide adequate care, the community must meet the need.

THE COMMONWEALTH'S HEALTH PROGRAM

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GOOD health has always been one of man's most prized possessions. From the most primitive times he has endeavored to take advantage of such knowledge as was available to him in prolonging his life, in preventing disability and in avoiding sickness. Believing that disease was of demonic origin he employed various mystic incantations in an attempt to ward off and to cure illness. The Mosaic laws contain the first rudimentary development of a definite sanitary code. Not until relatively modern times, however, could advantage be taken of accurate scientific knowledge in the prevention of disease, the prolongation of life and the attainment of optimal health.

Massachusetts has always been one of the pioneers in the field of public health. About two hundred years ago, Boston passed its first ordinance for the purpose of quarantining ships entering the harbor from ports where diseases such as yellow fever and smallpox were prevalent. Approximately twenty-five years later, the ubiquitous Paul Revere, who not only completed his famous ride but also made George Washington's false teeth, became chairman of Boston's first board of health. In 1869 the first state department of health in this country was created in Massachusetts. Since then, official health departments have been extended throughout the entire country.

* * *

In medical care, Massachusetts has also taken the lead and has supported certain phases of so-called "state medicine" for over a hundred years. At present there are no less than seven departments of the state government taking an important role in medical care. Of primary significance are the boards of registration that, through the licensing of doctors, dentists, pharmacists and nurses, attempt to ensure quality in medical practice. Unless there are adequate standards for practitioners, there cannot be adequate medical care. Although the Approving Authority for medical schools has now made it impossible for graduates of unapproved schools to take examination for licensure in the Commonwealth, it must be remembered that, in Massachusetts, approximately fifteen hundred graduates of substandard schools are at present engaged in active practice.

Two groups are interested in the medical care of the worker in industry. The Industrial Accident Board is concerned with the medical and hospital care of workers injured on the job, whereas the Division of Occupational Hygiene in the Depart-

ment of Labor and Industries studies the health hazards that the worker encounters.

The Department of Public Welfare not only maintains the State Infirmary at Tewksbury and the Massachusetts Hospital School at Canton for the custodial care of crippled and deformed children but also finances the medical care of indigent persons suffering from diseases that are not communicable. The Vocational Rehabilitation Program, under which any person of legal employable age who is totally or partially incapacitated for remunerative occupation may obtain assistance, administered by the Department of Education. In case of financial need, the corrective medical, surgical or psychiatric treatment required to make it possible for the patient to obtain employment is provided. For example, if a man has a hernia that interferes with his ability to work, he may have it repaired. The Department of Mental Health, which has perhaps the largest financial stake in medical care, provides treatment for the mentally ill and the mentally defective in its various institutions.

The last group concerned is the Department of Public Health, which, almost from its inception has had a considerable stake in the problem of medical care. The first tuberculosis and cancer hospitals to be maintained at state expense were started in Massachusetts. Hospitalization of tuberculous patients is recognized as an integral part of a tuberculosis-control program. Immediate care is essential. If "red tape" holds up the hospitalization of a patient with tuberculosis, the chances of its spread among contacts is increased, and the likelihood of recovery is materially reduced. It is a well known fact that 85 per cent of tuberculosis cases can be arrested if treated in time. A major problem in the care of tuberculous wage earners is that frequently no provision is made to assure an adequate standard of living for their families. Steps are now being taken, however, to correct this deficiency.

State sanatoriums for the treatment of cancer patients are provided at Pondville and Westfield. The Department of Public Health also maintains twenty co-operative cancer clinics, at which the physicians give their services without compensation. These are essentially diagnostic clinics, since no operations are performed and no extensive radiotherapy is given. As in cases of tuberculosis and other communicable diseases, immediate care is vital. Experience has shown that the disease can

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Health agencies is done outside the official governmental agencies."

In planning for the future the voluntary health agency must discover for itself how it can advance public health. Thus, such an organization has a definite responsibility to assist in making community surveys of existing institutions and of other facilities for the improvement of the health of the people. In promoting its own activities and functions an agency must be cognizant of the work of other agencies to avoid duplication and overlapping. Moreover, it is essential that all voluntary health agencies begin to co-ordinate their programs so as to discharge their responsibilities more efficiently.

* * *

There are several immediate needs for public-health programs in Massachusetts. The first of these is the strengthening of the official agencies — namely, the state and local departments of health. A health department must be able to function free of political interference if it is to carry on its duties efficiently and on the basis of scientific knowledge. Thus, the health commissioners should be appointed by the Public Health Council rather than by the governor or the mayor of a city. They should be assured of some security of tenure and should not be subject to the turnovers that often follow a change in political regime. They should likewise be assured of reasonable compensation — one that would provide them with a standard of living equal to that of other leaders in medical practice in their communities. Their staffs should have similar protection and whenever possible they should be protected by Civil Service laws and should receive higher compensation than that received at the present time by practically all health department employees in the Commonwealth. As a matter of fact, in many health departments, there is a dearth of physicians and other professional personnel because of the comparatively low salaries paid these employees. It is therefore necessary that the Massachusetts Medical Society and other professional groups lend their support to the common effort of raising salaries for health-department employees in the Commonwealth. The professional salaries of the Massachusetts Department of Public Health personnel, which were set back in the 1920's, have not been changed, except for wartime increases. If state and local health departments are not able to obtain and to hold well trained personnel, the quality of public-health work will greatly depreciate, and this will enhance the politicians' opportunities to dispense jobs and federal grants not on merit but on any opportunity to favor his chances of election.

Local health departments must obtain adequately paid full-time personnel who do not engage in private practice and must form into town unions. They are to make available, to the citizens, the benefits of the latest developments in public

health. This calls for the unification of boards of health into a common board that would employ a full-time, specially trained public-health physician with an adequate staff of full-time professional assistants. The time is past when public-health administration can be considered a part-time activity or a field to which physicians who have conducted a full-time general practice can retire on reaching old age. To make possible the formation of town unions on a permanent basis legislation at first permissive and later compulsory may be necessary. This should provide for a state subsidy, to be made available to town unions for the operation of such health departments. This is the procedure that is already effectively carried on in many states.

Voluntary health agencies should support the official health departments not only in the obtaining of more adequate funds but also in the passage of proper legislation and in the strengthening of the departments that are sorely in need of adequate personnel and facilities. In the past, voluntary health agencies, by passive acquiescence rather than by active support, have often gone along with health departments and have not assumed their proper share of the responsibility.

Doctors, nurses, other professional workers, lawyers, bankers, civic leaders and representatives of all groups interested in health should band together and form community health councils. These councils not only should survey their communities to determine the facilities that are available for health and medical care but also should ascertain the needs of the communities and assist in formulating plans to meet such needs. The health councils should also co-ordinate the work of the various agencies, assist in the avoidance of duplication and help in the provision of more complete coverage most efficiently to expend the public funds collected through either taxation or voluntary contribution. Finally, community health councils, working with the assistance of the medical profession and health department, should develop continuous health education programs designed not only to keep the public informed on health matters but also to obtain public support for health programs.

By the strengthening of the official health agency by obtaining health departments free from political interference, by providing personnel adequately trained, secure in office and properly compensated, by co-ordinating the work of all the voluntary health agencies and by receiving the support of the public professional groups and civic leaders, public health in Massachusetts can attain the desired objective of all those interested in the health and welfare of the people — namely, optimal health. Only by this concerted and continued active support of all interested can this goal of optimal health be attained.

REFERENCES

1. Cunn, S. and Platt, P. S. *Voluntary Health Agencies An Interpretive Study*. 364 pp. New York: Ronald Press Company, 1941.
2. Mustard, H. S. *Governments in Public Health*. 219 pp. New York: Commonwealth Fund, 1945.

Similarly, the patient who is ill with a disease such as diabetes or cancer is primarily responsible for his own care. If he neglects his own health, however, either wilfully or because of lack of means, and becomes a burden on the community in that he is no longer self-supporting and his dependents are potential welfare charges, the health of the patient becomes the concern of the community. It assumes the responsibility for his care, so that he will not remain a continued liability but will again become an asset — independent, self-supporting and contributing to the public welfare.

Under the Constitution of the United States, the responsibility for the health and welfare of the people rests officially with the state and not with the federal government. The state may delegate this responsibility to its political subdivisions. In Massachusetts, the responsibility has been delegated to the state and local boards of health and of public welfare. Although there is an excellent health department on the state level, health departments have failed to provide the people with adequate health services on the local level. The provision of adequate health service, which is now a primary responsibility of health departments, can be attained only through the organization of permanent town unions. Each union should include about 30,000 people to provide for the employment of full-time, trained health workers. Since a minimum of approximately \$2.00 per capita is required for efficient health administration, a subsidy must be made available to these health departments from the state government. The local health department should be administered by a full-time physician not engaged in private practice. He should be advised by a board of health that has no executive authority. School health programs should be an integral part of the health department's function and closely co-ordinated with the other health activities.

* * *

The voluntary agency has a vital role in community health organization. Often, in our complex civilization, the official agency does not furnish all the facilities necessary to render complete and adequate care of the needy. The voluntary health agency can and should assume some of the burden by providing for the care of such groups of patients as are not included under the functions of the official agencies and by disseminating knowledge and promoting programs that increase the community's assets for the attainment of optimal health.

The voluntary health movement in the United States began about sixty years ago with the formation of the Pennsylvania Society for the Prevention of Tuberculosis. At that time this was an extraordinarily far-sighted step — one that was so far in advance of the times that it was not duplicated in other states for over ten years. A second state society was organized in Ohio in 1901, and a third in New York in 1902. The National Tuberculosis

Association was formed in 1904 and included twenty-three state and local organizations. These have increased to such an extent that at the present time there are over three thousand chapters in the United States. The most striking fact is the marked unevenness of the voluntary movement. There are over twenty thousand voluntary health agencies — some excellent, but others inadequate. I think it developed spontaneously to meet new recognized needs in a variety of neglected fields. The movement has lacked over-all direction and planning. The time is ripe for stocktaking and for developing sounder programs. Many of the present activities of volunteer societies should properly be absorbed by the official health departments, which, after all, are the responsible health agencies. There is therefore a need for increasing the co-ordination of effort on national, state and local levels. In fact, some authorities have advocated the unification of one strong organization of all the related health promoting voluntary agencies in a city or in a state with appropriate emphasis on the various aspects of a unified health program. Such authorities as Gunn and Platt¹ recommend "the pooling of the present separate competitive and confusing appeals of the voluntary national health agencies into a unified nationwide campaign effective on the local, state and national levels, along the lines already proved to be acceptable to the American people through the National War Fund in conjunction with the community chests."

On the other hand, certain groups are interested in promoting a compulsory health program administered by the federal government that would, to a large extent, sound the death knell of many of the voluntary health agencies. Even if the eventual taking over of all the technical services for public health by official agencies could be visualized, four important functions of the voluntary public health agencies would remain.

In the first place they would remain the guardian and watchdog of the official health departments. Voluntary organizations of alert and informed citizens, sensitive to the community's need in public health, can serve at all times to defend, strengthen, criticize, support and assist the official agency as servant of the public. Such organizations would always take an active interest in promoting health legislation in all levels of government. They are needed, especially if national in scope, to stimulate and finance research. Finally, they have a continuing educational function. They can develop machinery for supplementing official health and educational organizations and can augment the efforts of professional groups to popularize scientific knowledge bearing on health.

Voluntary health agencies are here to stay. A. Mustard² stated in a recent publication, "It requires only casual study of the situation to learn that a great deal of work important in maintaining public

penicillin an acid substance. The explanation was that the ionized forms of the basic drugs (streptomycin) compete with the hydrogen ions, and those of the acid drugs (penicillin) compete with hydroxyl ions, for position on the cell surface. Since tissue damage is accompanied by an increase in the local acidity, a concentration of a basic drug, such as streptomycin, that is effective in blood may be inadequate to destroy bacteria in local lesions.

The importance of alkalization of the urine during streptomycin therapy is brought out in a recent report by Kane and Foley¹¹ presenting the results of treatment in 38 cases of pyelonephritis and 2 cases of cystitis due to gram-negative bacilli. Most of the patients had previously been treated with sulfonamides, mandelic acid and penicillin. The duration of the infection in each case had varied from weeks to years. Seventy-five per cent of patients were cured, and 10 per cent showed improvement. It is noteworthy that several of the cured patients had small renal calculi, and others had moderate structural deformities. The failure in 15 per cent could be attributed in each case to the fact either that marked structural deformity was present or that the concentration of streptomycin necessary to inhibit the growth of the infecting organism was higher than could be obtained in the urine with the dosage employed. The authors attribute the more favorable results obtained in their series, as compared with those of others, to the fact that the urine in each case was rendered alkaline during therapy.

Certain toxic reactions may occur during treatment with streptomycin. These are chiefly sensitization reactions with skin eruptions and fever, vertigo and tinnitus.⁶ If a skin rash appears, it is advisable to stop streptomycin or continue treatment with care. In patients on prolonged courses of streptomycin, vertigo has been the most troublesome symptom, but many patients apparently overcome the subjective symptoms in spite of continued treatment. Tinnitus is considered a warning signal to decrease the dosage.

Although the streptomycin therapy of certain pyogenic infections of the urinary tract has been given at least a moderate trial and appears to be effective in many cases, particularly those due to gram-negative bacilli, its usefulness in renal tuberculosis is less clearly defined. This is because it soon became evident that long courses of treatment were necessary and supplies of streptomycin were limited. There is some evidence, however, that streptomycin is helpful in this disease. The results in 12 patients with genitourinary tuberculosis treated with streptomycin at the Mayo Clinic were sufficiently encouraging to make further trial interesting.¹² Although the patients were probably not treated for sufficiently long periods, a temporary beneficial effect was obtained in a reasonable number of cases. Pyuria was decreased, vesical symptoms were improved in some and the number of

tubercle bacilli in the urine was said to have decreased. Bladder ulcerations healed in a case of renal infection treated over a long period and reported by Allea.¹³ There are no reports of streptomycin therapy in cases of early renal tuberculosis.

TESTICULAR NEOPLASMS

Hormonal tests for the diagnosis and prognosis of testicular neoplasms were in general use ten or twelve years ago. Indeed, a classification of these tumors was advocated at one time on the basis of quantitative determinations of the gonadotropic hormone in the urine.^{14, 15} These tests have been largely abandoned because of inconsistent results. Embryonal carcinomas, teratomas and seminomas—all of them malignant—frequently gave negative tests before operation. It soon became evident, moreover, that the tests did not always provide an accurate index of the subsequent course of the disease. Many patients with advanced metastatic lesions gave negative tests.

Brewer¹⁶ recently reported 2 cases of primary testicular neoplasms. The histologic diagnosis in one was teratoma, and in the other, seminoma. The metastases in both cases, however, were chorioepitheliomas. When each patient was first seen tests for chorionic gonadotropin in the urine (Friedman and Aschheim-Zondek tests) were positive. It was believed that although chorionic tissue had not been demonstrated histologically in the primary tumor, it must have been present, since chorionic gonadotropin was present in the urine and the metastases were chorioepitheliomas. Small areas of chorioepithelioma may have been present in the primary tumor but not detected on microscopic examination because the entire tumor was not examined or because it may be difficult to differentiate chorionic tissue from the varied tissues composing a testicular neoplasm.

That two distinct types of gonadotropin reactions occur in tests with testicular tumors is pointed out by Brewer. These reactions represent two different gonadotropic hormones. One is the chorionic type of gonadotropin, identical with that formed in the urine of pregnant women, it produces luteinization in the ovarian follicles of test animals. The second type of gonadotropin is the castrate type elaborated in the pituitary gland. This hormone is present in the urine of male or female castrates, in women past the menopause and in elderly men. It produces follicle growth but not luteinization in the ovaries of test animals.

It is necessary to distinguish between these two reactions when testing for tumors of the testis, and failure to do so has caused confusion in the correlation of the test and the type of tumor. Brewer considers the presence of chorionic gonadotropin in the urine to indicate the presence of a biologically active tissue, whereas the presence of castrate type of gonadotropin means merely a reduction or cessation

MEDICAL PROGRESS

UROLOGY

FLETCHER H COLBY, M D *

BOSTON

THE following is a review of recent studies on the use of streptomycin in urologic infections, testicular neoplasms, retroperitoneal tumors and necrotizing renal papillitis

STREPTOMYCIN

Considerable progress has been made in recent years in ability to control infections of the urinary tract. Mandelic acid, the sulfonamides and penicillin have played a role in the problem, and during the past year another preparation has become available for this purpose. In 1944 Schatz, Bugie and Waksman¹ first described the isolation of a new antibiotic agent that they named "streptomycin." Animal experiments demonstrated the low toxicity of this agent and its effectiveness against infections due to gram-negative bacilli.²⁻⁵ Since any one of these preparations is chiefly effective against certain groups of bacteria, or even strains of bacteria, the value of the identification of the infecting organism has become increasingly clear. The sensitivity of the bacteria to the therapeutic agent has also become an important consideration.

The method of preparation and directions for the administration of streptomycin are given in a report of the Committee on Chemotherapeutics and Other Agents of the National Research Council.⁶ Streptomycin is available as the sulfate salt or the hydrochloride salt. Both salts are readily dissolved in distilled water or isotonic sodium chloride solution. Concentrations of 100 to 175 mg of streptomycin per cubic centimeter of solution are prepared for intramuscular injection. Enough solution should be used so that the preparation is clear and free of undissolved particles. The total volume should be as small as possible. The expiration date of vials of streptomycin is eighteen months after release. The drug should be kept in the refrigerator. Intramuscular injection is the method generally employed for urinary-tract infections. Maximum serum levels of streptomycin are reached within one to three hours after intramuscular injection, and additive effects are obtained by a repetition of the dose every three or four hours. Most of the streptomycin is excreted from the blood into the urine by the kidneys.

Four hundred and nine cases of infection of the urinary tract are included in the report by the Committee on Chemotherapeutics and Other Agents

All cases were resistant to the sulfonamides, many varieties of bacteria were represented. Many of the patients were given daily intramuscular injections of solutions containing 1 or 2 gm of streptomycin for five to seven days, with an average total dose of 7.5 to 10 gm. Many infections were of longstanding. The over-all recovery rate in this series was 42 per cent. It was concluded that it was difficult to assess the relative merits of streptomycin in this group of infections, but many of the patients were improved, without recurrences. Mixed infections did not respond so well as those due to a single organism. A rapid development of resistance by bacteria to streptomycin was observed, and was thought that this accounted for many cases of failure to sterilize the urine. The favorable effect of streptomycin on infections due to *Proteus* species in this series should be noted.

A rapid increase in resistance to streptomycin organisms infecting the urinary tract appears to be a major problem, and this fact merits careful consideration in the future treatment of patients with such infections. Sensitivity tests in vitro seem to be a reasonable guide to treatment. The rapidity with which organisms can acquire resistance to streptomycin is emphasized in a report from the Boston City Hospital by Finland et al.⁷ and by others.⁸ The former showed that in 8 carefully observed cases of urinary-tract infection a considerable degree of resistance to streptomycin was acquired by the infecting organisms within a short time. Repeat tests of organisms isolated before treatment showed them to be sensitive in vitro, whereas those obtained after treatment were highly resistant and the patients failed to respond to apparently adequate doses of streptomycin. It has been stated that dosage should be guided by the sensitivity of the organisms and that, when possible, an adequate concentration of streptomycin should be maintained in the blood and tissues to inhibit the growth of organisms.⁹ It was thought that in this way the resistance to streptomycin could be reduced. For urinary-tract infections a daily dose of 1 to 3 gm for five to ten days was recommended.⁶

Streptomycin is most effective in an alkaline medium. This fact was observed by Schatz, Bugie and Waksman¹ and confirmed by Abraham and Duthie.¹⁰ Differences as great as tenfold were encountered between activities measured at reaction of pH 6.0 and pH 8.0. The reverse was true of

*Chief Urological Service, Massachusetts General Hospital

penicillin an acid substance. The explanation was that the ionized forms of the basic drugs (streptomycin) compete with the hydrogen ions, and those of the acid drugs (penicillin) compete with hydroxyl ions, for position on the cell surface. Since tissue damage is accompanied by an increase in the local acidity, a concentration of a basic drug, such as streptomycin, that is effective in blood may be inadequate to destroy bacteria in local lesions.

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of testicular function. As applied to testicular tumors, then, the chorionic gonadotropin is the more important hormone, and its presence in the urine is detected by the usual tests of pregnancy.

The results of orchidectomy and external irradiation in 80 cases of malignant testicular neoplasm by Nesbit and Lynn¹⁷ give a survival rate of 24 per cent. The patients were followed for a minimum of four years. It is pointed out that an occasional patient of this sort with metastases has survived long enough to be fairly regarded as cured. Two patients with proved metastases have lived for eleven and twelve years following treatment with no evidence of recurrence. Four patients lived from four to six years and then died of the disease, so that any study based on a four-year follow-up is considered subject to approximately a 10 per cent error. Only about a third of the cases reported by Nesbit and Lynn showed a significant elevation in prolan level. Removal of the tumor and postoperative — not preoperative — irradiation are favored by the authors.

A surprisingly high incidence of testicular tumors was found in the armed forces. Vermooten¹⁸ attributed this to the easier access to medical advice, frequent examinations and the rigors of training. He explained the low incidence of metastases by the earlier diagnosis made possible because of these facts. Others, however, reported a high incidence of metastasis (24 per cent) among soldiers when first seen with testicular neoplasms and discouraging results after treatment.¹⁹ No correlation was demonstrable between the results and the duration of the disease before treatment or the type of tumor.

From 1940 to 1946 the Army Institute of Pathology collected 922 cases of tumor of the testis from Army patients.²⁰ Over 96 per cent of these neoplasms fell into the following classifications: seminoma (germinoma), 35 per cent, embryonal carcinoma, 19 per cent, and chorioepithelioma, 0.4 per cent, teratoma, 7 per cent, and teratocarcinoma, 35 per cent. Clinically as well as histologically the seminomas were less malignant than the embryonal carcinomas, and the authors expressed the opinion that these tumors differ not only in fundamental cell type but also in biologic behavior and prognosis.

Fully differentiated chorioepitheliomatous tissue was present in about 6 per cent of embryonal carcinomas, and the hemorrhagic necrosis and vascular invasion characteristic of chorioepitheliomas were frequently seen in the embryonal carcinomas. Pure primary chorioepitheliomas accounted for less than 0.4 per cent of the tumors. The fact that chorionic gonadotropin is often present in the urine of patients with so-called "embryonal adenocarcinoma" is considered to provide physiologic substantiation for the morphologic observation that many embryonal carcinomas are trophoblastic tumors. The new term "teratocarcinoma" is proposed to include the large group of pleomorphic tumors in which both differen-

tiated teratoid structures and histologically malignant elements are present.

An interesting feature of this group of tumors was that the death rate and incidence of metastasis were practically the same for the adult teratomas and the teratocarcinomas, supposedly because a teratocarcinoma matured into an adult teratoma after malignant embryonal cells had already been disseminated to other parts of the body. A study of the histologic components of the primary tumor and the metastases showed that 90 per cent of the embryonal carcinomas metastasized as embryonal carcinomas or chorioepitheliomas and that 40 per cent of the metastases of teratocarcinomas were embryonal carcinomas or chorioepitheliomas. It therefore appears obvious that any of these tumors may display chorioepitheliomatous tissue in their secondary deposits. Whereas only 0.4 per cent of these tumors were pure chorioepitheliomas, 27 per cent of all the metastases in cases that terminated fatally contained chorioepithelial elements. This excellent report deserves the attention of all who are interested in tumors of the testis.

In a study of testicular neoplasms in dogs Huggins and Pazos²¹ found that atrophy of the prostate was present in all tumors except the interstitial-cell variety, in which the prostate was normal or enlarged. The authors present evidence that the interstitial-cell tumors arose from the Leydig cells and that the tubular adenomas originated from the cells of Sertoli. They also confirmed previous observations that seminomas arose from the germinal epithelium.

Most of the recent reports on tumors of the testis emphasize what has long been regarded as an important feature in their management. This is ligation of the spermatic cord high in the inguinal canal and removal of the affected scrotal contents through this incision without opening the tunica vaginalis. This procedure lessens the likelihood of local recurrence from tumor-cell implantation. In a recent case of a highly malignant testicular tumor in our own experience, the hydrocele fluid associated with the neoplasm was found to contain many tumor cells in the stained smear.

RETROPERITONEAL TUMORS

Tumors that arise independently in the retroperitoneal tissues are not frequent but are of considerable interest. This group of neoplasms concerns both the general surgeon and the urologist, since the outstanding sign is often an unexplained abdominal mass, and the close relation of the mass to the kidneys and ureters is apt to deform or displace these organs. Past references concerning primary retroperitoneal tumors have not been complete. All the available information about these tumors is presented by Donnelly,²² with a report of 95 cases observed during the past twenty years at the University of Iowa Hospitals.

The retroperitoneal space is described as between the lumbar and iliac regions and between the peritoneum and the posterior parietal walls of the abdominal cavity. The tumors originate within this space behind the posterior peritoneum. They may take origin from the urogenital ridge fatty or connective tissue, lymphatic vessels or sympathetic nervous tissue. As they enlarge, they displace the abdominal viscera and may involve the mesentery of the large or small bowel. The tumors may be benign or malignant and occur at any age. The wide diversity of cell types of retroperitoneal tumors was once explained on the basis that they arose from remnants of the urogenital apparatus.²³

Primary retroperitoneal neoplasms have varied considerably histologically. Sarcomas were regarded as the most frequent of the malignant tumors and lipomas as the most frequent of the benign types. The nonmalignant tumors are said to be potentially malignant and prone to recur. Even the lipomas when they occur retroperitoneally have a tendency to undergo malignant change with recurrence and death. This tendency to recur is also true of other usually benign tumors when retroperitoneal—namely fibromas and leiomyomas. The explanations given for this fact are that small outgrowths of these tumors are overlooked and not removed at operation and that the tumors contain sarcomatous elements not readily identified histologically.

Retroperitoneal cysts represent a type of these tumors. They have been classified as cysts of urogenital origin, teratomatous cysts and lymphatic, traumatic and parasitic cysts. They are most frequent in women from fifteen to twenty-five years of age and usually occur on the left side. The preoperative diagnosis is apt to be ovarian cyst.²⁴

Of the 95 cases of primary retroperitoneal tumors in Donnelly's²⁵ series 82 were classified as malignant, and 13 as benign. Sarcoma, fibrosarcoma and undifferentiated neoplasms, such as embryoma and adenocarcinoma, were the most frequent accounting for 81 per cent of the malignant tumors. Epithelial cysts were the most frequent benign tumors.

Gastrointestinal symptoms predominated in the patients with retroperitoneal neoplasms. Indefinite abdominal pain in the lower abdomen, nausea, constipation and anorexia were the usual complaints. Some patients noted the presence of an abdominal mass. As the mass increases in size, the symptoms are those resulting from pressure on adjacent structures. Symptoms had averaged over nine months before these patients sought treatment.

Patients with retroperitoneal tumors usually presented diagnostic problems. Gastrointestinal x-ray films and retrograde pyelograms assisted in the making of a correct diagnosis before operation. When these steps had been omitted the preoperative diagnosis had usually been ovarian tumor in the women and cancer of the gastrointestinal tract in men.

The treatment of these tumors is exploratory abdominal operation with removal of the tumor mass if possible. Eighty-two of the patients in this series were operated on. Forty-eight, or 65 per cent, were found unsuitable for surgical removal. Twenty-eight patients received deep x-ray treatment, and 77 per cent of the tumors were considered radio-sensitive. Best results were obtained when complete surgical excision of the tumor was possible. An operative mortality of 20 per cent indicates the hazard of surgery in patients with primary retroperitoneal tumors.

NECROTIZING RENAL PAPILLITIS

An interesting and usually fatal type of suppurative pyelonephritis that is frequently but not always, associated with diabetes is described by Robbins, Mallory and Kinney.²⁶ The pathologic characteristics of this condition are abscesses in the renal pyramids with sufficient extension to cause necrosis of the terminal portion and suppuration and gangrene of the renal papillae. In most of the cases death was directly attributable to a necrotizing papillitis. Miscellaneous organisms are involved. Clinically this lesion should be suspected in severe acute urinary-tract infections in diabetic and non-diabetic patients with urinary obstruction, particularly in the presence of oliguria and a rising non-protein nitrogen. In the later stages of the disease pyelographic changes may be present.

REFERENCES

1. Schatz A, Bueie E and Waksman S A. Streptomycin substance exhibiting antibiotic activity against gram positive and gram negative bacteria. *Proc Soc Exper Biol & Med* 55:66-69 1944.
2. Robinson H J, Smith D G., and Graessle O E. Chemotherapeutic properties of streptomycin. *Proc Soc Exper Biol & Med* 57:226-231 1944.
3. Jones D, Metzger H J, Schatz A and Waksman S A. Control of gram negative bacteria in experimental animals by streptomycin. *Science* 100:103-104 1944.
4. Hellman F R. Streptomycin in treatment of experimental tularemia. *Proc Staff Meet Mayo Clin* 19:553-559 1944.
5. *Idem*. Streptomycin in treatment of experimental infections with micro-organisms of Friedlaender group (Klebsiella). *Proc Staff Meet Mayo Clin* 20:339 1945.
6. Committee on chemotherapeutics and other agents. National Research Council. Streptomycin in treatment of infections: report of one thousand cases. *J A M A* 132:447 and 70-77 1946.
7. Finland M, Murray R, Harris H W, Kham L and Meads M. Development of streptomycin resistance during treatment. *J A M A* 132:16-20 1946.
8. Bondi A Jr., Ottenberg D, Detz C C and Brown C L. Streptomycin therapy in infection of urinary tract: failure because of development of resistance. *J A M A* 132:64 1946.
9. Knop C Q. Experimental study of resistance to streptomycin by some bacteria commonly found in urinary infections. *Proc Staff Meet Mayo Clin* 21:235-236 1946.
10. Abraham F P and Duthie E S. Effect of pH of medium on activity of streptomycin and penicillin and other chemotherapeutic substances. *Lancet* 145:459 1946.
11. Kane L W and Foley G F. Role of streptomycin in treatment of 2 cases of bacterial infection. *J A M A* (in press).
12. Cook E N, Greene L F and Hinchshaw H C. Streptomycin in treatment of tuberculosis of urinary tract. *Proc Staff Meet Mayo Clin* 21:277-280 1946.
13. Alvea E P. Personal communication.
14. Ferruson R. S. Quantitative behavior of prolan A in teratoma testis. *Am J Cancer* 18:269-295 1935.
15. *Idem*. Pathologic physiology of teratoma testis. *J A M A* 101:10-19 1933.
16. Bower I I. Chorionic gonadotropin in diagnosis of testicular tumors. *Proc Staff Meet Mayo Clin* 21:280-291 1946.
17. Verbit R M and Lynn J M. Treatment of malignant testicular neoplasms and analysis of 19 cases. *Urology* 1:44-45 1946.

- 18 Vermooten, V. Testicular tumors *Arch Surg* 50 63 66 1945
- 19 Lowry, E. C., Beard, D. E., Hewitt, L. W., and Barner, J. L. Tumor of testicle analysis of 100 cases preliminary report *J Urol* 55 373 384, 1946
- 20 Friedman, N. B., and Moore, R. A. Tumors of testis report on 922 cases *Mil Surgeon* 99 573 593 1946
- 21 Huggins, C., and Paxon, R., Jr. Studies on tumors of testis morphology of testicular tumors of dogs *Am J Path* 21 299 309, 1945
- 22 Donnelly, B. A. Primary retroperitoneal tumors report of 95 cases and review of literature *Surg Gynec & Obst* 83 705 717 1946
- 23 Hansmann, G. H., and Budd, J. W. Massive unattached retroperitoneal tumors explanation of unattached retroperitoneal tumors based on remnants of embryonic urogenital apparatus *Am J Path* 7 631 673, 1931
- 24 Handfield-Jones, R. M. Retroperitoneal cysts their pathology, diagnosis, and treatment *Brit J Surg* 12 119 134, 1924
- 25 Robbins, S. L., Mallory, G. H., and Kinney, T. D. Necrotizing renal papillitis form of acute pyelonephritis *New Eng J Med* 235 885 893, 1946

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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EDITH E. PARRIS, *Assistant Editor*

CASE 33171

PRESENTATION OF CASE

A sixty-six-year-old Canadian housewife was admitted to the hospital for the fourth time because of recurrent pain in the right upper quadrant.

Two years before admission occasional attacks of sharp pain in the right upper quadrant had begun, sometimes originating at about the anterior axillary line and radiating to the epigastrium and substernal region. At other times the pain originated in the epigastrium and radiated to the right, along the lower costal margin to the infrascapular region. Radiation was also described as at times going into the right shoulder. These attacks recurred at monthly intervals and had become more frequent in the past year, sometimes only a few days apart. A year before admission a physician told the patient that she had gall-bladder trouble and started her on bile salts and a fat-free diet. She had been forced to call her physician frequently for the pains in the right upper quadrant, which were relieved by pills taken by mouth. At times these attacks of pain were associated with chills. During the attacks she became nauseated and sometimes vomited. She had considerable gas and had been constipated about a year, obtaining relief with mineral oil. About a month before admission her daughter noted that the patient had become yellow, but this had not increased in intensity and the patient thought that it had decreased. The stools had been clay colored but later were brown. She had been losing weight despite a fair appetite, falling from 220 pounds in 1936 to about 150 pounds at the time of admission.

The first admission to the hospital had been thirteen years previously because of a tumor in the right breast of five months' duration. This had proved to be carcinoma, and a radical mastectomy had been performed. The axillary lymph nodes

were not involved. The patient did well until ten years later, when she again complained of tenderness and an indefinite tumor in the upper outer quadrant of the left breast, suggesting cystic disease. She was readmitted about eight months later, after considerable urging, and a left radical mastectomy was performed for another breast carcinoma. No involvement was seen in the axillary lymph nodes. About a year and a half after the second operation a firm oval nodule developed on the left that was slightly tender and adherent to the skin but not to the chest wall. This was excised and diagnosed as recurrent carcinoma. The patient then did well until six years before the present admission, when she noticed a small lump on the tip of the tongue. This increased slightly in size until all the teeth were extracted, when the lump began to decrease and subsided to the point where it was not necessary for her to return. Letters stated that she was well. A year prior to admission she had pneumonia and was confined to bed for three weeks at home and treated with sulfonamides and penicillin. She also stated that for the past twelve years she had had high blood pressure. Otherwise, she had no cardiac symptoms other than ankle edema in the evening, which had been present for about thirty years. She had also noted occasional palpitation and moderate exertional dyspnea.

Physical examination revealed a well developed, well nourished, slightly jaundiced woman lying quietly in bed in no acute discomfort. There was no evidence of recurrence in either of the mastectomy scars, and the chest was clear to percussion and auscultation. The heart did not appear to be notably enlarged. A Grade II, harsh systolic murmur was heard in both the apical and the aortic areas and transmitted to the neck, but the aortic second sound was not obliterated. There was no thrill. The abdomen was soft and obese, with moderate tenderness to pressure in the right upper quadrant in the midclavicular line, but no spasm and no masses. The liver was not palpated. There were minimal osteoarthritic changes of the distal phalanges of both hands. Over the ninth and tenth dorsal vertebrae there was a subcutaneous, freely movable, nontender mass, measuring 3 by 3 cm., that was apparently a collection of adipose tissue.

The temperature, pulse and respirations were normal. The blood pressure was 220 systolic, 95 diastolic.

Examination of the blood disclosed a hemoglobin of 104 per cent and a white-cell count of 6250. The urine gave a ++ test for albumin, with a questionably positive test for bile. The stools were pale brown and guaiac positive. An electrocardiogram was described as showing sinus arrhythmia, with auricular premature beats, a rate of 46, a PR interval of 0.16 second, a QRS of 0.06 second, normal voltage, a tendency to left-axis deviation, a notched S₂, upright T waves in Leads 1, 2 and 3 and in Leads CF, CF₁, and CF₂, and slight sagging of the ST segment in Lead CF₃. X-ray studies of the chest and abdomen revealed no notable abnormality, no calculi were recognized in the abdomen. A bromsulfalein test revealed 28 per cent retention of the dye. The blood phosphorus was 3.7 mg, the non-protein nitrogen 28 mg, the cholesterol 294 mg and the cholesterol esters 130 mg per 100 cc, and the alkaline phosphatase 20.9 Bodansky units. The prothrombin time was normal. A van den Bergh test was 1.6 mg per 100 cc direct and 2.2 mg indirect. The total protein was 7.46 gm per 100 cc, with an albumin-globulin ratio of 1:3. A cephalin-flocculation test was negative in twenty-four hours and ++ in forty-eight hours.

On the fourth hospital day a peritoneoscopy was negative. Two days later intravenous pyelograms and a barium enema were essentially negative. The liver was noted to be somewhat enlarged, slightly depressing the hepatic flexure. On the next day a gastrointestinal series revealed a 5-cm, sharply demarcated, nodular tumor mass arising from the lateral aspect to the body of the stomach, a repeat bromsulfalein test revealed 20 per cent retention of the dye. On the twelfth hospital day a gastroscopy was performed, revealing a slightly atrophic antrum with a tightly closed, pale, normal pylorus. On the greater curvature, just proximal to the angulus, there was a nodular, polypoid, mulberry reddish-purple, easily bleeding mass about 4 by 4 cm in diameter and somewhat spherical in shape. It seemed to be wholly confined to the greater curvature. Toward the anterior wall the mucosa was pale and numerous blood vessels were easily visible.

Two weeks after admission cholecystectomy was performed with exploration of the common duct. At operation multiple small calculi, measuring up to 8 mm in diameter, were found in a chronically thickened gall bladder. The common duct measured 10 mm in diameter and was explored without the finding of a stone. Two masses in the head of the pancreas were biopsied and frozen section revealed chronic pancreatitis. The body and tail of the pancreas were irregular and nodular, the individual nodules measuring up to 20 mm in diameter. None of these were thought by the surgeon to be typical of carcinoma. The gastric lesion measured roughly 5 cm in diameter and was apparently attached to the greater curvature half way between the angulus

and the cardiac end of the stomach. There were three small, tiny, lymphatic nodules and subserous lacteals in the greater curvature over the base of the tumor, but the lesion was thought to be resectable from the abdomen. On the day following cholecystectomy a bilateral prophylactic superficial-vein interruption was done, and about a month after admission a subtotal gastrectomy was performed.

DIFFERENTIAL DIAGNOSIS

DR CLAUDE E. WELCH: The first part of this history is a fairly definite story of gall-bladder disease probably on the basis of common-duct stone because of the repeated attacks and the fact that the common-duct obstruction had been intermittent in type, as evidenced by the stools. The only feature that we cannot explain well on the basis of gall-bladder disease is the rather marked loss in weight.

Dr Fav assures me that these electrocardiograms are essentially normal.

This patient had some type of jaundice. The evidence points definitely toward obstruction of some type, as indicated by the high alkaline phosphatase. There is also evidence of a certain amount of liver damage as shown by retention of bromsulfalein, although it was not marked because of the normal prothrombin time. There were moderately elevated cholesterol and cholesterol ester levels, whereas the van den Bergh reaction showed evidence of slight jaundice. The flocculation tests were equivocal. All the heart studies, I should say, indicate that the patient was a good preoperative risk — almost anyone who walks around is a good risk, I understand. The x-ray film showed something that was not expected. May we see the film?

DR RICHARD SCHATZKI: Do you want to see the stomach film?

DR WELCH: I want to spend more time on that than on anything else.

DR SCHATZKI: We have one film not a spot film, on which the mass that was described can be seen.

DR WELCH: Can you tell about the margins of the tumor?

DR SCHATZKI: From this film I assume that it was a polypoid mass in the lumen of the stomach.

DR WELCH: You do not wish to say whether this area on the other side is normal?

DR SCHATZKI: In this film I think that I can see the upper edge of the mass. I cannot see the lower edge which must be hidden by barium. On the plain film of the abdomen the lower edge of the liver appears rather low laterally but the liver edge is quite sloped and I do not dare to guess its size. I suspect, however, that the liver is a little enlarged but with the liver edge so sloped as this a moderately low liver does not mean much.

This is the intravenous pyelogram. The dye is not well concentrated, but I cannot see anything wrong with the kidneys.

The chest film shows the area of the missing breast on the left side, and there is no evidence of metastases.

DR WELCH: The surgeon was faced with quite a problem—a known tumor of the stomach and a pathologic process in the biliary tract. Which should be attacked first, or should he be brave or foolhardy and attempt to do both at once? I assume that the wiser choice was taken in this case, because the patient had a low liver function and it was better to have the biliary tract functioning well before attempting gastric resection. The operation was probably done with the view of relieving the jaundice.

The empty common duct probably surprised the surgeon, and he undoubtedly explained it by saying that stones had passed through the common duct.

Many years ago, when Dr. Richard C. Cabot conducted these conferences, he put all his eggs in one basket and stated one diagnosis, which he made to cover all the findings. In these days, perhaps because the general incidence of older patients is so much higher, we consider ourselves lucky if we have such a thing as an uncomplicated carcinoma of the stomach. Obviously, in this patient it is impossible to make a single diagnosis to cover all the lesions. In the first place, the main problem that arises is that of the diagnosis of the stomach tumor, which may have been a primary tumor in the stomach, a recurrence of the carcinoma of the breast or a carcinoma of the pancreas that had been overlooked and had metastasized to the liver and to the stomach. The x-ray studies are helpful in that regard, because they rule out, for all practical purposes, any metastatic lesions. For an isolated metastasis to the stomach from carcinoma of the breast to show up six years after the last metastatic nodule had been observed would be queer indeed. Metastasis to the stomach from carcinoma of the pancreas is almost unknown, and a metastatic lesion of the stomach from either source that presented this x-ray picture would be impossible. We are therefore left with a discussion of the primary tumors of the stomach that can produce such an x-ray picture and give these findings by gastroscopy.

Before I saw this x-ray film I could not make up my mind regarding the exact type of tumor. Quite a list crossed my mind, such as fibrosarcoma, neurogenic sarcoma and leiomyosarcoma, all of which are frequent and produce spherical masses in the stomach, as well as an ectopic pancreas or lymphosarcoma. All these tumors were ruled out by the x-ray picture, which is not typical of any of them. We are restricted, practically speaking, to whether the lesion was a malignant polyp or a polypoid carcinoma. The gastroscopic picture does not help

us a great deal in this regard. I should like to know whether any induration was noted around the base of the tumor, but I assume that there was none, since it would have been mentioned.

So far as the question of a gastric polyp or gastric carcinoma is concerned, Drs. Benedict and Allen* looked up these lesions many years ago. They found that 40 per cent of the entire group were carcinoma. The diagnosis perhaps could have been aided by a smear of the gastric sediment to determine if any abnormal cells were found. As it is, I shall have to guess that, because the tumor was large, the stools contained occult blood and the patient had lost a fair amount of weight, we are dealing with a carcinoma rather than with a polyp of the stomach.

My diagnoses are carcinoma of the stomach, gallstones and chronic pancreatitis.

DR TRACY B. MALLORY: Dr. Robertson, will you give the opinion on the ward regarding the selection of procedures?

DR CHARLES W. ROBERTSON: Dr. Welch went through exactly the same reasoning we did on the ward. The patient was a hypertensive woman with known obstructive jaundice and a gastric lesion. The x-ray film that we have here is, I believe, one of the later films that were taken between the two operations. On the first film of the stomach we were impressed by the nearness of the lesion to the cardia of the stomach and the possibility of mucosal extension of the tumor to the esophagus, and for that reason we seriously considered exploration through the chest. That is why the statement was made at the first operation that the tumor was resectable abdominally. The findings at the first operation were exactly as the record described them—namely, a chronic pancreatitis and a chronically inflamed gall bladder, with evidence that the patient had probably been passing small calculi. The jaundice cleared up quickly following drainage of the common duct. The stomach was then resected abdominally, two and a half weeks later.

CLINICAL DIAGNOSIS

Gastric carcinoma?

DR WELCH'S DIAGNOSES

Carcinoma of stomach
Cholelithiasis
Chronic pancreatitis

ANATOMICAL DIAGNOSES

Multiple polypoid carcinomas of stomach, with metastasis
Chronic cholecystitis
Chronic pancreatitis

PATHOLOGICAL DISCUSSION

DR MALLORY: At the second operation a subtotal gastrectomy was done, and a large polypoid

*Benedict E. B. and Allen A. W. Adenomatous polypi of stomach. Surg. Gynec. & Obst. 58:79, 1934.

tumor with central ulceration was found. To one side of that and separated from it by a strip of apparently normal-looking mucosa was a second polypoid tumor. Whether this represented two separate malignant lesions of the stomach or whether one was an extension of the other, it is impossible to say. It is quite possible that there were two separate tumors. Both were malignant histologically and one or the other of them had led to a minute metastasis to a single lymph node, which we eventually found after sectioning a number of them.

DR WELCH: An excellent reason for delaying the operation until after the biliary tract had been explored is the fact that polypoid carcinoma is relatively slow to metastasize.

DR MALLORY: Dr Schatzki, have you any further comment?

DR SCHATZKI: So far as the tumors are concerned on the film, one can see only the upper edge of the larger lesion. The rest is merely barium.

CASE 33172

PRESENTATION OF CASE

A fifty-one-year-old housewife entered the hospital because of jaundice.

Three and a half months before admission the patient had noted the onset of anorexia and epigastric distention. Six weeks before entry generalized pruritus began. On two occasions the temperature was elevated to 99.2 and 99.4°F. Dark urine was noted a month before entry, and a week later definite jaundice appeared. With the onset of the jaundice the stools became light yellow. The patient believed that she had lost 10 to 15 pounds in the six months preceding admission. No unusual intolerance to fatty food had developed, but she had always avoided them because she thought that they caused hyperacidity. She denied using alcohol or drugs. Two months before admission and again a month later, she had visited a sister who was hospitalized with infectious hepatitis.

Except for a single attack of rheumatic fever in childhood, the past history was noncontributory.

On examination the patient was thin and fretful. The skin and scleras were yellow. Over the bridge of the nose there were several telangiectases. The lungs were normal. An early Grade II diastolic murmur was heard at the apex. The liver edge, which was palpated 4 cm below the ribs in the anterior axillary line and 8 cm below the xiphoid, was smooth, firm and nontender. The tip of the spleen was palpable on deep inspiration. The uterus was normal rounded and about the size of an orange.

The temperature was 98°F, the pulse 89, and the respirations 19. The blood pressure was 140 systolic, 80 diastolic.

Examination of the blood revealed a hemoglobin of 13.2 gm per 100 cc and a white-cell count of

11,000, with 72 per cent neutrophils. The urine was cloudy and orange. The specific gravity was 1.020, there was no albumin, sugar or bile, but urobilinogen was present in a dilution of 1:80, there were 6 epithelial cells per high-power field in the sediment. The stools were tan to light grayish tan. A guaiac test was + on two occasions, and negative on one. The total protein was 6.9 gm per 100 cc, with an albumin-globulin ratio of 1:4 and the cholesterol was 208 mg, the nonprotein nitrogen 21 mg, the vitamin A 70 mg, the carotenoid 40 mg, and the alkaline phosphatase 7.7 Bodansky units per 100 cc. The serum bilirubin was 4.2 mg per 100 cc direct and 5.6 mg indirect. The cephalin-flocculation test was negative after twenty-four hours and + after forty-eight hours. The prothrombin time was 13 seconds (control 15 seconds). A plain film of the abdomen was normal. There was no filling of the gall bladder during the Graham test.

In the hospital the patient continued to have slight itching, moderate jaundice and a normal temperature. On the third day the serum turbidity test* was 4.3 units at the end of thirty minutes and the thymol flocculation test was ++++ at forty-eight hours.

On the thirteenth day the phosphatase was 11.3 Bodansky units per 100 cc, the phosphorus 3.5 mg, the bilirubin 5.8 mg direct and 7.5 mg indirect. The prothrombin time was 19 seconds (control 16 seconds). Five milligrams of bromsulfalein per kilogram of body weight injected intravenously showed 30 per cent retention of the dye in forty-five minutes.

The liver remained about the same size. Subsequently the jaundice increased slightly, and the stools became definitely clay colored and were only slightly positive for bile. On the twenty-fifth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR ALLEN G. BRAILEY: This case illustrates a frequent and often puzzling problem—the cause of jaundice. Jaundice is the visible expression of hyperbilirubinemia, which in turn may be caused by increased blood destruction or by inability of the damaged liver to excrete the bile adequately. The first possibility—namely, that this patient had hemolytic jaundice—seems out of the question. In its favor are the absence of bile in the urine and some evidence of enlargement of the spleen, but the course of the disease was not that of acholuric jaundice. No familial history of this condition was obtained, and tests for spherocytosis and increased fragility of red cells were not done. Obviously, the service did not consider hemolytic jaundice, and I think that we should not do so either.

It is much less easy to dispose of the suggestion that the patient had some form of intrahepatic parenchymal disease. For example, the entire course

*Neefe J. R. Results of hepatic test in chronic hepatitis without jaundice: correlation with clinical course and liver biopsy findings. *Gastroenterology* 57:119, 1946.

is not inconsistent with infectious hepatitis. The onset was rather protracted, but such an onset certainly occurs. It is thrown in for good measure that her sister had been hospitalized with infectious hepatitis. This patient's illness, however, appears to have antedated exposure to her sister's infection. She had had jaundice for a total of at least six weeks, but that is not an unusual duration, nor is it unusual for the jaundice to be getting worse instead of better at the end of such an interval. It is reported that at the end of six weeks the stools became definitely clay colored, and this ought to mean, if she had hepatitis alone, that the liver cells were so severely damaged that they were no longer secreting bile. Opposed to such a notion is the rather remarkable lack of evidence of parenchymal damage. We are presented with an impressive array of liver-function tests but for the most part they were all within normal range—the total protein, the albumin-globulin ratio, the cholesterol, the cephalin flocculation, the vitamin A and the prothrombin time. The thymol-turbidity test gave a borderline result and points, but only uncertainly, to liver-cell disease. Since I believe that there is too little evidence of liver-cell disease as the primary trouble, I rather reluctantly relegate hepatitis of any sort to second place.

A better possibility seems to be that the jaundice was due to biliary obstruction. This would adequately account for all the laboratory data presented. In fact, the ratio of direct to indirect serum bilirubin is some slight evidence for jaundice on an obstructive basis. But was the obstruction due to stone within the lumen of the duct or to pressure, presumably from cancer, without? I am sure that there is no way in which we can resolve this question with any certainty. Without doubt, a stone is a real possibility, and it is easy to make the mistake of attaching too much importance to the slender clues that the record contains in favor of cancer. For instance, the fact that the patient had no pain is statistically slightly in favor of cancer. The tip of the spleen was felt. This may occur with either type of obstruction, but again it is a little more frequent with cancer. The clinical course was quite steadily progressive over a total of nearly five months—a picture at least consistent with cancer. Dr. David Riesman used to consider preicteric itching suggestive evidence of malignant obstruction. The liver edge appeared to be abnormally low. One cannot make much of that. It may have been merely ptotic, but if it was really enlarged, it appears not to have enlarged rapidly, for it was said not to have been tender.

Since I must make a diagnosis I shall vote for biliary obstruction due to cancer—the cancer being primary in the pancreas, the ampulla, the gall bladder or even the liver itself. The cancer may have been metastatic, provided the metastasis happened

to develop at the porta hepatis. In addition, the patient probably had rheumatic heart disease and enlargement of the uterus due to fibroids.

It is stated that on the twenty-fifth day an operation was performed. The possibilities of a benign and remediable condition are excellent, and the patient's condition certainly indicated a liver biopsy and probably an exploratory laparotomy.

DR. CLAUDE E. WELCH: Since Dr. Brailey made a diagnosis of cancer, I should like to ask him if he could be more specific. If the surgeon is going to explore, it makes a difference whether the lesion is primary or metastatic. From the history, I think that one can be more specific.

DR. BRAILEY: On a statistical basis, cancer of the head of the pancreas is the most probable, but I should be glad to have you tell me.

DR. WELCH: The gall bladder was not palpable, which is distinct evidence against cancer of the head of the pancreas.

DR. BRAILEY: The patient was a fairly thin person, and the gall bladder might have been expected to be palpable. I do not attach significance to the Graham test. Do you think that nonvisualization is in favor of carcinoma of the gall bladder?

DR. WELCH: No, I do not believe so, because she was deeply jaundiced. No mass was palpable that could be distinctly felt as carcinoma of the gall bladder. She could have had carcinoma of the duct, but that is all she could have had of that nature.

DR. DANIEL S. ELLIS: At the time the Graham test was done, the patient was barely jaundiced. The jaundice seemed to be fading.

DR. BRAILEY: That gives a slightly different picture. I had the impression that she had a fairly steady course.

DR. ELLIS: That is the reason the Graham test was done at the time. Clinically there was enough change to indicate that she seemed to be getting better, and we thought that we might get more evidence from it.

DR. TRACY B. MALLORY: An attempt was made to get additional information on this patient by liver biopsy, which I believe was rather more confusing than helpful. Dr. Ellis, will you take up the story?

DR. ELLIS: This case was one that makes liver disease so fascinating to work with. When the patient was first seen in the office about two weeks before admission to the hospital, the history seemed to be more consistent with a diagnosis of cancer than anything else. One was struck by how well she looked. The stools when first seen were light tan, and she had bile in the urine. I elected to follow her for two weeks at home, the stools became dark, and the degree of jaundice stayed about the same. The itching for practical purposes ceased. At the end of that period, it was believed that there had been no real improvement and that the diagnosis was still not proved. Accordingly, she was admitted to the hospital for aspiration liver biopsy. The tests

referred to above were done on admission, and on the fourth day a biopsy was performed. On the basis of this biopsy report, which Dr. Mallory will describe, we thought that she had intrahepatic disease. The palpable spleen lent more evidence to this diagnosis, and there was no question that the spleen was large enough to be palpable. Largely on the basis of the biopsy report, we elected to give medical treatment for two more weeks.

DR. MALLORY: The aspiration biopsy showed an unusual appearance on which I could not make a diagnosis. The liver cells were obviously abnormal. A portion of them were fat containing, and some were markedly vacuolated but showed a hydropic type of vacuolization rather than that due to fat. That is an unusual finding in biopsy material, and I do not know how to interpret it. There was scanty inflammatory infiltration in the portal areas. I was unable to make a diagnosis of infectious hepatitis, but I did think that there was intrinsic liver disease of some unknown character. That was as far as we were able to go at that time.

DR. ELLIS: On that basis we gave intensive medical therapy, but at the end of two weeks three factors were obvious: the patient was no better, the jaundice was marked, and the stools were clay colored, lighter than before. So far as the laboratory evidence was concerned, she had a rising phosphatase, which bothered us considerably. She started with a low phosphatase but before operation it was up around 15 units. Since she had had the best treatment that we could give her and was getting worse, we decided to perform an exploratory laparotomy. Preoperatively all of us believed that she had intrahepatic disease, the basis of which we hoped would be some obstructive phenomenon that had given rise to an ascending infection and a biliary cirrhosis or ascending cholangitis, although there was a good probability that we would find cancer somewhere.

DR. MALLORY: Dr. McKitterick, can you tell us something about the operation?

DR. JOHN B. MCKITTERICK: I was not present at the operation, which Dr. Leland McKitterick performed. The findings were somewhat unusual in one respect—the patient had a completely col-

lapsed external biliary tree. The gall bladder was just as though one had aspirated it and erupted it of all bile. The common duct was so small that it was almost impossible to get a needle into it. Two or three masses were palpable on the dome of the liver, which to Dr. McKitterick did not feel like metastases. The liver itself was somewhat reddish. The spleen was enlarged. There was some white scarring that was palpable throughout the liver. In the left half of the pancreas, there was a definitely palpable tumor. The liver was biopsied, as was the tumor in the pancreas.

CLINICAL DIAGNOSIS

Carcinoma of pancreas?
Intrahepatic disease?

DR. BRAILEY'S DIAGNOSES

Biliary obstruction, due to carcinoma
Rheumatic heart disease

ANATOMICAL DIAGNOSES

Adenocarcinoma of pancreas, with liver metastases
Biliary cirrhosis of liver, slight

PATHOLOGICAL DISCUSSION

DR. MALLORY: Biopsy of the liver showed that, in the interval between biopsy and operation, the vacuolization of the liver cells, both fatty and hydropic, had entirely disappeared, presumably as the result of the dietary treatment that Dr. Ellis had carried out. In one respect, however, namely, bile stasis, there was no improvement, in fact this was considerably intensified. Bile staining of the Kupfer cells was particularly prominent. The portal areas had become wider, and in many of them we found strands and small clumps of frankly neoplastic cells. Biopsy of the pancreas showed an adenocarcinoma, which was undoubtedly the primary site of the neoplastic disease.

I do not believe that I can explain the collapse of the extrahepatic bile ducts with any certainty. The widespread tumor infiltration of the portal areas within the liver may have produced obstruction of the small intrahepatic bile ducts.

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

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MATERIAL should be received not later than noon on Thursday, two weeks before date of publication.

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COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

DIAGNOSIS OF AMEBIASIS BY STOOL EXAMINATION

DURING the past year the results of several studies on dysentery and diarrhea in members of the armed forces returning from tropical areas have been published.^{1,2} These indicate to some extent the number of persons who had these diseases while overseas. The majority of these men are no longer in the service, and a certain percentage are being seen by clinicians because of unexplained persistent diarrhea, diarrhea alternating with constipation or vague abdominal symptoms.

Since a variety of causes can be responsible for these intestinal conditions and since the clinical symptoms are frequently nonspecific, it is necessary to find an organic basis or a pathogen responsible

for the condition, with subsequent elimination of the latter if discovered. Although clinicians can explore the physiologic bases for these symptoms by routine procedures and although reliable stool cultures for pathogenic bacteria are readily obtained, there is a scarcity of laboratory technicians skilled for the diagnosis of infections due to intestinal parasites.

The majority of human helminthic infections have a definite geographic distribution. For example, a person who has never been outside New England could not have filariasis or hookworm infection, but a man with a period of wartime service on certain Pacific islands might have become infected with both these helminths. Thus, knowledge about the patient's travels and the conditions under which he lived in endemic areas is helpful in arriving at the possibility of infection and the specific helminthic infection suspected. Unfortunately, infection with *Endamoeba histolytica*, the causative agent of amebic dysentery, is universal, although it is more prevalent in the tropics than in the temperate zones. Consequently, infection with this organism can take place anywhere, if food or water contaminated with the infective cysts is ingested.

In examining a stool for parasites, the technician must be able to recognize not only various stages of the pathogen but also nonpathogenic organism, tissue cells, macrophages and debris. A reliable diagnosis is not readily obtainable because the majority of laboratory technicians are not properly trained or lack the necessary equipment. It is a rare technician who can make a satisfactory diagnosis by following a textbook or laboratory manual. Morphology of the organisms, staining technics and cultural procedures must be learned and mastered. Indeed, practical experience gained during a period of intensive training is usually necessary if the technician's results are to be reliable. In addition, the clinician, intern or nurse should know that fecal samples for examination should be free of antiseptics and urine and should be delivered to the laboratory within an hour. If the stool cannot be examined immediately, it should be placed in the refrigerator, not in the incubator. Furthermore, normally passed stools are preferable if the laboratory technician is not highly skilled. Purged stools

give a higher percentage of positive results, but the presence of tissue cells and macrophages may confuse the novice

Textbooks of clinical pathology, parasitology and tropical medicine give the usual procedures for the recognition of amebas in stools. These include a record of the gross appearance of the specimen, including the presence or absence of mucus, pus or blood. Microscopical examination of a fresh preparation consists of a search for active stages of the protozoa or their cysts, as well as tissue cells, erythrocytes and *Blastocystis hominis* (a nonpathogenic, yeast-like organism). If cysts are present, a presumptive diagnosis can often be made by the examination of an iodine-stained preparation, but films stained by the iron-hematoxylin method are usually required to make a specific diagnosis. Cultivation of the specimen for *E. histolytica* is a useful supplementary procedure, but it is not considered practical for routine laboratory purposes unless the technician has had experience with this technic. Concentration methods, using a saturated solution of sodium chloride or zinc sulfate flotation, are satisfactory for the detection of nonoperculated helminthic eggs and of low concentrations of cystic amebas. It must be remembered, however, that such methods are useful only to detect the cystic stages, not the active stages, which are present in patients with acute amebic dysentery and in a certain percentage of carriers. The complement-fixation test has been improved and is sometimes used to detect the presence of infection with *E. histolytica*, having proved particularly valuable in suspected cases of hepatic amebic infection. It requires skill, and only a few laboratories are equipped to make the test.

Interpretation of negative or positive findings should depend on the clinical symptoms of the patient. Amebas are not passed at a constant rate in the feces, so that a negative finding in one or several specimens does not necessarily mean that the patient is not infected, nor should it invalidate the results of other laboratory examinations. If suspicion of infection with *E. histolytica* persists, additional stool specimens should be examined. Proctoscopic or sigmoidoscopic examination is helpful in recognizing ulceration in the lower bowel. If ulceration is present, scrapings from the crater of

the ulcer should be examined, since this is the likeliest place for the presence of *E. histolytica*. Furthermore, a positive diagnosis for *E. histolytica* in the absence of symptoms indicates that the patient is a carrier, and the organism should be eliminated by a course with an amebicidal drug, because of the danger of transfer of amebas to others.

The above statements have been made not with the view to create alarm regarding the incidence of amebiasis but to point out the need for improved training of hospital laboratory technicians in the performance of stool examinations for the presence of amebas, to discuss briefly the conditions required for a reliable diagnosis and to point out the meaning of positive and negative findings.

REFERENCES

1. Marion D. F. and Sweetser F. N. Amebiasis in military overseas returnees. *Am J Trop Med* 24:186-191 1946
2. Kenamore B. Chronic diarrhea in military personnel returning from the tropics. *Bull U S Army Med Dept* 7:121-124 1947

THE QUALITY OF MERCY

THE ancient Israelites, who first conceived the idea of one god for all people, were also the first to credit that Being with absolute justice stern as it might be, and later with the quality of mercy. Mercy, so far as we know, had been a scarce commodity in the world up to that period. Sapient man had been in existence for three or four hundred centuries but he had lived by the law of a tooth for a tooth and an eye for an eye and precious little mercy had entered into it.

Mercy, which Webster considers to be "forbearance from inflicting harm; compassionate treatment especially of the suffering or helpless," is an emotional attribute that might be considered almost spiritual. Rarely, if ever, can it be conceded to lower forms of life, yet few men can be believed to be utterly without it.

Animals show only rudimentary social emotions. They care for their young or destroy them, the dog risks his life for his master or languishes on his grave, they hunt in packs. Certain insects lead highly organized community existences and lend mutual aid, as do bees and ants and wasps but except occasionally for the dog to his master or perhaps mated pairs to each other animals do not know the emotion of compassion. That has been reserved for man.

Shakespeare has given us our greatest dissertation on mercy, which, as we all know, "blesseth him that gives and him that takes" The scepter of a king, we are told, shows the might of temporal power

But mercy is above this temporal sway,
It is enthroned in the hearts of kings,
It is an attribute to God himself,
And earthly power doth then show likest God's,
When mercy seasons justice

We had believed, until a few short years ago, that man might be on an upward path, that his moral insight might be keeping pace with his intellectual achievements, but we have learned since then that ethical conduct depends on certain little understood and unreliable factors Too often in man's history it has happened that just as he reached a point in progress where he thought that he might pause and pose for the photographers, at that point the shooting began Man can apparently become without compassion

So the inhabitants of the world find themselves again resuming the search for the causes of man's inhumanity to man Those who are aware of the need are doing it as individuals, as groups, as nations and as organizations of nations Among the leaders in the search must be the men and the professions among men that, knowing most about suffering, have chosen to be greatest in compassion

The profession of medicine, freed to a large extent from mystery and magic, has shown itself for centuries to be the calling of the Samaritan It has combed the battlefield unarmed, seeking only to lighten suffering where it might be found Its followers are in a position where, by themselves and through their organized fellowships, they must expect to share leadership, to set examples and to stir consciences in still another attempt to shape man's destiny according to a pattern of universal tolerance and mercy

OBITUARY

CHARLES FAIRBANKS PAINTER

1869-1947

Dr Charles F Painter died suddenly at his home on January 6, 1947 He was a direct descendant of an old Virginia family, although he was born in Grand Haven, Michigan, on May 19, 1869

On graduating with a degree of A B in one of the earliest classes of the newly founded Johns Hopkins University in 1891, he came to Boston and studied medicine at the Harvard Medical School, receiving the degree of M D in 1895 He was a member of the first four-year class at Harvard Medical School, where he was associated with such well known classmates as Joseph A Capps, Arthur L Chute, E Amory Codman, Harvey Cushing, Elliott P Joslin, Timothy Leary, William H Robey and Franklin W White Harvey Cushing was closely associated with Charles Painter during his four years at the medical school, and it was Cushing who wrote in a letter to his father dated January 31, 1892 "Painter, I like very much He is slow, but hangs on to everything he gets He hails from Great Barrington and is a great big solid whole-souled creature such as one likes to meet."

He served his internship at the Massachusetts General Hospital and later served at the old Children's Hospital, where he was associated with E H Bradford, Robert Lovett and other brilliant orthopedic pioneers of the time He himself became an outstanding orthopedic surgeon and engaged in active practice of this specialty For many years he was surgeon-in-chief at the Carney Hospital

Between 1913 and 1922 he was dean of Tufts College Medical School This was the decade of World War I, with all the turmoil created by that conflict in the field of medical education, and this service indicates Dr Painter's administrative capacity He also had strong literary interests and was always ready to serve on committees or otherwise when these interests could be brought to bear on current problems While dean at Tufts Medical School he created a Chair of the History of Medicine and occupied it himself for a number of years He edited the *Yearbook of Orthopedic Surgery* and served for a long time on the editorial board and briefly as editor of the *Journal of Bone and Joint Surgery* He was president of the American Orthopaedic Association in 1915 and 1916

In 1929 Dr Painter was chosen librarian of the Boston Medical Library, in which position he served until 1937 He continued the high standards of the Library although it was his lot to hold this position during a period of decreasing financial support That he was able to prevent any material reduction of service to the Library members and the public under these circumstances indicates his devotion to the things that the Library stands for and to the Library itself

Dr Painter's death closes the life of a man who was a scholar as well as a physician and surgeon and who became one of the foremost orthopedic surgeons of his day He was a devoted student of medical history and literature, and one may well understand Cushing's comment that he was "a solid whole-souled creature such as one likes to meet"

H R V

MASSACHUSETTS MEDICAL SOCIETY

ANNUAL MEETING OF THE COUNCIL

The annual meeting of the Council will be held in the Georgian Room of the Hotel Statler, Boston, on Monday, May 19, 1947, at 7:00 p.m. This meeting will be preceded by the Cotting supper, which will be served in Parlors A and B of the same hotel at 6:00 p.m.

Business

- 1 Presentation of record of the stated meeting of the Council held February 5, 1947 as published in the *New England Journal of Medicine* issue of April 17, 1947
- 2 Reports of standing and special committees
- 3 Election of officers and orator
- 4 Appointment of committees for ensuing year
- 5 Such other business as may lawfully come before the meeting

MICHAEL A. TIGHE, Secretary

NEW HAMPSHIRE
MEDICAL SOCIETY

DEATHS

GREELEY—Philip H. Greeley, M.D. of Dover died December 20, 1946. He was in his seventy-seventh year. Dr. Greeley received his degree from Dartmouth Medical School in 1897. He was a fellow of the American Medical Association.

His widow and two sons survive.

SPRAGUE—Fred A. Sprague, M.D. of Concord died December 3, 1946. He was in his seventy-fourth year. Dr. Sprague received his degree from Baltimore Medical College in 1906. He was a veteran of both the Spanish American War and World War I. He was a fellow of the American Medical Association.

His widow, two sisters and a brother survive.

MISCELLANY

A BORDEN AWARD TO DR. GAMBLE

The Borden Awards, which were established in 1936 by the Borden Company Foundation, Incorporated, to recognize and encourage outstanding research achievements in the United States and Canada, are administered by eight professional and scientific associations, each of which annually selects someone to receive the award who has reported notable research in his particular field.

To the American Academy of Pediatrics is delegated the responsibility of selecting an investigator who has performed outstanding research in the nutrition of infants and children, and for the year 1946 it chose Dr. James L. Gamble, professor of pediatrics at Harvard Medical School and visiting physician at the Children's Hospital, Boston. The citation reads: "For pioneer work over a period of many years in the field of salt and water balances in the human body with particular reference to infants and children."

CORRESPONDENCE

DEPRIVATION OF LICENSES

To the Editor: At a meeting of the Board of Registration in Medicine held March 21, it was voted to suspend the registration to practice medicine of Dr. Frederick J. Butler, 166 Townsend Street, Roxbury. Dr. Butler was cited to a hearing under General Laws Chapter 112, Section B, but was unable to appear because he is a patient at the Boston State Hospital.

At the same meeting, the Board also voted to revoke the registration to practice medicine of Dr. David Ginsburg,

1938 Main Street, Springfield, following his conviction in court of having performed an abortion.

H. QUIMBY GALLUPE, M.D., Secretary
Board of Registration in Medicine

State House
Boston

DDT "POISONING"

To the Editor: The report of a case of periarthritis nodosa, by Drs. William R. Hill and C. Robert Damiani, which appeared in the December 19, 1946, issue of the *Journal*, was read with considerable interest. It was an able and convincing presentation of a case of that rare and little understood disease. If it had been presented as such, it would have been much less sensational, but at the same time would have been a positive rather than a negative contribution to medical knowledge.

The title and conclusions add one more item to the list of source material that has deluded these authors and will delude still others into erroneous diagnoses of DDT poisoning. Such an erroneous diagnosis in itself may well be the cause of fatalities, for example, the man in New Jersey who developed a constricting pain in the chest while spraying DDT. His doctor, believing that DDT was highly poisonous, advised the victim to run up and down out of doors and breathe deeply in the fresh air. The man followed this advice and proceeded to die, but in the face of a history of a preceding coronary heart attack, the preliminary newspaper reports of a DDT fatality were corrected and did not become a part of medical literature.

The circumstances surrounding the exposure to DDT in the present case deserve careful consideration.

(1) The total amount sprayed in the workroom was 150 cc of 6 per cent DDT and presumably the largest portion of this was sprayed hours before the man came to work. No hand sprayer is made which will keep more than a fraction of 1 per cent of the atomized DDT from settling on the walls or floor, either at the moment of spraying or within a few minutes thereafter.

(2) Even with aerosol atomizers, a very large portion settles out quickly and the remainder could not by any stretch of the imagination have concentrated itself in the lungs or on the skin of the victim in a quantity of the magnitude of 1 per cent of the total which he himself sprayed.

(3) This should be recognized as an infinitesimal dose, even from the most carelessly studied cases of DDT poisoning cited. Reference to the works of Neal et al. should be given considerably more weight than the others cited because of a vastly greater background of toxicologic experience, and because Neal's studies are particularly thorough and scientific investigations of DDT toxicology.

The low toxicity of DDT is attested by a wide experience with its use. I have seen men spraying scores of gallons of DDT a day indoors, day after day, and know of men who have done this for upward of a year. I have seen mixing by hand of thousands of gallons of oily solutions of DDT day after day with frequent wetting of arms and hands, with no ill effect.

The supposition that this patient had become sensitized is not supported in any way, not even by history of prior exposure. Tremors are a sign of acute toxicity, develop early and disappear with recovery. In the case cited, tremors did not develop until a month after an insignificant exposure, and a few days before death in a disease affecting the blood vessels of the brain. The offering of tremors as evidence of the validity of the DDT assumption in this case is an indication of faulty logic as well as a misunderstanding of the true toxicity of DDT. This misunderstanding should not be propagated.

This comment is properly divided into two parts. No slightest exception is taken to the clinical, laboratory and pathological description of a death due to periarthritis nodosa. But the title "Death following Exposure to DDT" is considered misleading and false in its implication. The reasoning is based on false and inadequate premises of exposure and known toxicity of DDT. The assumption, repeated in the conclusion, that DDT was the probable cause of the fatal disease in this case and the statement "It is reasonable to assume that DDT possesses allergenic properties and should be included among the drugs capable of producing a sensitizing reaction" are entirely unjustified.

Of all possible explanations of the present case, this one is the most highly imaginative and quite likely to cause harm and confusion in the medical literature

R W BABIONE
Captain (MC), U.S.N

413 Tyler Place
Alexandria, Virginia

Captain Babione's letter was referred to Dr Hill, whose reply is as follows

To the Editor Perhaps the title of this paper is somewhat misleading since death could not be primarily attributed to DDT. Nonetheless, the clinical picture was quite consistent with a sensitization reaction, and the fact that this became manifest less than twenty-four hours after exposure to DDT makes the latter the presumptive exciting agent. The finding of the lesions of periarthritis in the biopsies of the skin and muscle is further evidence of an allergic reaction. It is well known that sensitization may result from infinitesimal amounts of allergenic agents

WILLIAM R HILL, M D

520 Commonwealth Avenue
Boston

BOOK REVIEWS

Diseases of the Skin By George C Andrews, M D Third edition 8°, cloth, 937 pp, with 971 illustrations Philadelphia and London W B Saunders Company, 1946 \$10.00

Dr Andrews has thoroughly revised this new edition of his standard textbook on dermatology. Almost every paragraph has been revised by the deletion of obsolete material and the addition of recent discoveries. Treatment with the sulfonamides, penicillin, streptomycin and other antibiotics has been incorporated throughout the text. Discussions of more than sixty new skin diseases have been added. New chapters have been inserted with the intention of aiding those who desire to take the examinations of the American Board of Dermatology and Syphilology. All prescriptions have been rewritten in the metric system and in Latin so far as practicable. Many new illustrations have been added. The *Standard Classified Nomenclature of Disease*, compiled by the National Conference, has been followed, with minor exceptions. Every effort has been made to keep the classification simple, easy to use and practical. The text is well written and well organized. Special prominence is given to the more frequent dermatoses. A selective bibliography is appended to each chapter. The text is well printed with a good type on good paper, and the illustrations are adequate. This book should be in all medical libraries and should prove useful to all physicians interested in diseases of the skin.

Electrocardiography in Practice By Ashton Graybiel, M D, and Paul D White, M D With the assistance of Louise Wheeler, A M, and Conger Williams, M D Second edition 8°, cloth, 458 pp, with 323 illustrations Philadelphia W B Saunders Company, 1946 \$7.00

This new edition has been revised in the light of recent advances in the subject. A new section on precordial leads has been added in the first part, and illustrations of normal and abnormal multiple precordial electrocardiograms have been introduced throughout the text. The fifth part contains a new series of test electrocardiograms presented in random fashion, for practice in interpretation. Two new topics, unipolar and esophageal leads and the effects of exercise and low oxygen tests, have been added in appendices. Four new tables are of special interest: the first shows the effects of the so-called "indifferent electrode", the second tabulates the disorders of rhythm, the third shows the characteristic changes in the electrocardiogram in various diseases affecting the heart, and the fourth lists the changes resulting from the administration of various drugs and the effect of various physiologic influences. The usefulness of multiple chest leads is fully discussed.

This standard monograph should be in all medical libraries and should prove of value to all physicians interested in diseases of the heart.

Electrocardiography, including an Atlas of Electrocardiograms By Louis N Katz, M D Second edition, thoroughly revised 4°, cloth, 882 pp, with 525 illustrations Philadelphia Lea and Febiger, 1946 \$12.00

The author has thoroughly revised this standard work, bringing up to date the subject matter and the bibliography and rewriting large portions of the text. The additional material has increased the size of the volume about 50 per cent, necessitating the division of the text into twenty-three chapters instead of the sixteen in the previous edition. The illustrations have also been completely revised, one hundred and twenty-five having been deleted and two hundred and forty nine added. Summary tables and new charts showing the salient features of normal and abnormal deflections, of specific patterns and of various arrhythmias have been introduced to make the volume more suitable for beginners. A third chest lead—Lead CF—is described, and its use under various circumstances considered and illustrated, because the author is convinced from his experience in over 5000 cases that this chest lead contributes greatly to the evaluation of abnormalities of the heart, especially of heart strain, intraventricular block and coronary disease.

The report of the special committee of the American Heart Association on the establishment of a universal nomenclature for the several deflections of the electrocardiogram is included, and its recommendations are largely followed with a few exceptions. A new chapter on terminology has been introduced. A section on the principles involved in the electrical manifestations of the heart has been added, and recent concepts of the theory of the electrocardiogram and findings on the properties of the heart have been included in the revision. War experience having shown that the variation in normal electrocardiograms was greater than supposed, the standards of normality have been completely revised and the effect of posture, body build and the physiologic state of the subject have been discussed in a separate section. The chapters on transient electrocardiographic changes in acute and chronic illness and in patients under the influence of drugs have been expanded to include recent information. The conditions giving rise to electrocardiograms simulating the coronary pattern are emphasized in a separate chapter, and coronary pain and coronary circulation have been included to make the subject of coronary disease more complete. The material on the management of cardiac arrhythmias and coronary disease has been expanded for the benefit of the clinician. A new chapter on interference and dissociation has been added, as well as material on several unusual and complex arrhythmias and new information on the nature of intraventricular block and the combination of the shortened PR interval and the prolonged QRS complex.

Despite these major additions and expansions the scope and purpose of the work have not been altered. A selective bibliography is appended to each of the three sections of the text. The book is well printed with a good large type, and the large number of tracings are uniformly clear and distinct. This treatise should be in all reference medical collections.

Nursing in Commerce and Industry By Bethel J McGrath, R N, for the National Organization for Public Health Nursing 8°, cloth, 356 pp New York The Commonwealth Fund, 1946 \$3.00

This volume provides a much needed authoritative up-to-date text in industrial nursing. Mrs McGrath is well qualified for the task of writing such a text, since she was formerly industrial nursing consultant to the National Organization for Public Health Nursing and is chief industrial nursing consultant to the American Association of Industrial Nurses and industrial nurse of the Powers Dry Goods Company, Minneapolis. The book has been planned for the nurse already practicing in the field.

Dr Alice Hamilton, well known authority on industrial poisons, has written an interesting and informative introduction in which she points out the great advances in industrial medicine and nursing that have taken place during the last thirty years. The material is well organized, and the text well written and documented.

The author defines industrial nursing as the application of nursing skill to groups of men and women at their places of work for the purpose of helping them build and maintain their best health, and the rendering of prompt and efficient nursing assistance when they become ill or injured.

The preliminary chapters are devoted to the history of industrial nursing in the United States, industrial organization, the nurse, the nurse's duties and responsibilities and physical facilities for the nursing service, as well as an important chapter on relations with employees and employee organizations.

Then in order follow discussions of the health of the worker, occupational accidents and hazards, disease hazards, non-occupational illness and accidents, mental hygiene, including malingering, sight conservation (written by Eleanor Mumford), orthopedic nursing (written by Katherine Ott), nutrition, problems peculiar to women in industry and the control of communicable diseases. The concluding chapters concerning records and reports were written by Heide L. Henniken, and those on rehabilitation, workmen's compensation, industrial welfare activities and hourly nursing service by an outside agency by Lucille M. Harmon.

An appendix contains important miscellaneous material including equipment for the health service, a concise manual for emergency procedure, a formula for an industrial cleanser, standards for maternity care and employment of expectant mothers, and equipment and technic for eye examinations.

The book is well printed with a good type on good soft paper and is not too heavy for the size of the volume. It has an adequate index. It should be in all medical, public-health and public libraries, as well as in all industrial and commercial libraries.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Cornell Conferences on Therapy, Volume I Edited by Harry Gold, M.D., managing editor, David P. Barr, M.D., Eugene F. DuBois, M.D., McKee Cattell, M.D. and Charles H. Wheeler, M.D. 8°, cloth, 322 pp. New York: The Macmillan Company, 1946. \$5.25.

The topics reported in these informal conferences, first held in 1937, cover the whole field of therapeutics and are a selection from a large number. The following subjects are discussed: the doctor's bag, use and abuse of bed rest, heart failure, digitalis vs. digitoxin, mercurial diuretics, subacute bacterial endocarditis, abdominal distention, intestinal infections, diseases of the eye, poisoning and the Rh factor.

A Textbook of Gynecology. By Arthur H. Curtis, M.D., professor and chairman of the Department of Obstetrics and Gynecology, Northwestern University Medical School, and chief, Gynecological Service, Passavant Memorial Hospital, Chicago. Fifth edition. 8°, cloth, 755 pp., with 455 illustrations, chiefly by Tom Jones. Philadelphia: W. B. Saunders Company, 1946. \$8.00.

This standard treatise has been extensively revised in all but a few chapters. The section on ovarian tumors has been expanded, and in the chapter on other tumors of the uterus, two new topics, sarcomatoid growth of the endometrial stroma and hypertrophy of the uterus, have been added. The endocrinographic disturbances have been co-ordinated into a separate division providing a consideration of the subject in its entirety. Penicillin therapy has been added to the topic of gonorrheal infection. A large number of new photographs and photomicrographs have been added to the text. The book is well printed with a good type on good paper. The illustrations are excellent. It is recommended for all medical libraries as a reference book.

English-French and French-English Technical Dictionary. By Francis Cusset. 16°, cloth, 590 pp. Brooklyn, N. Y.: Chemical Publishing Company, Incorporated, 1946. \$5.00.

This small dictionary with terms in two parts, French-English and English-French, is well organized and printed

with contrasting type on good paper. The text is not limited to single words but has a large number of short word combinations. It is recommended for all library reference collections.

Proceedings Conference on diagnosis in sterility. Sponsored by the National Committee on Maternal Health, January 26-27, 1945. New York City. Edited by Earl T. Engle, Ph.D. 8°, cloth, 237 pp. with illustrations. Springfield, Illinois: Charles C. Thomas, 1946. \$5.00.

The papers contained in this volume of proceedings cover the various aspects of human sterility. Among the topics discussed are semen examination, testicular biopsy, the role of the accessory glands, chronic hemospermia and its treatment with estrogen, endometrial biopsy, basal body-temperature curves, examination of cervical mucus, tubal-patency tests, history taking of infertile couples and a working hypothesis of the mechanism of sterility. The book is well published and is recommended for all medical libraries and for gynecologists and physicians interested in the subject.

Physiotherapy. By Thomas F. Hennessey, M.D., dean and director, Massachusetts School of Physiotherapy. Boston. 8°, paper, 25 pp. Boston: Bellman Publishing Company, Incorporated. 75 cents.

This outline is one of a series of seventy-five occupational booklets used in connection with guidance work. It discusses physiotherapy as a special field in its educational and vocational aspects.

Irish Medical Directory and Hospital Year Book—1945. Eighth edition. 8°, cloth, 296 pp., illustrated. Dublin: The Parkside Press Limited, 1946. 10 shillings, 6 pence.

This reference work is divided into three parts. The first is clinical and contains a number of special articles on delivery, abortion, cancer of the cervix, tuberculosis in infancy, rickets, diarrhea and social service in hospitals. The second comprises an alphabetical list of all physicians in active practice in Ireland, with their qualifications, hospital connections and important medical writings. The third is a list of hospitals in Ireland arranged by county and giving information concerning the administration, number of beds and nurses and public or private status.

Protozoology. By Richard R. Kudo, D.Sc., professor of zoology, University of Illinois. Third edition. 8°, cloth, 778 pp., with 226 illustrations. Springfield, Illinois: Charles C. Thomas, 1946. \$8.00.

This standard textbook first published in 1931, has been thoroughly revised and brought up to date. The chapters on physiology, reproduction and variation and heredity have been largely rewritten and enlarged. New material has been added on major groups and phylogeny, and on collection, cultivation and observation. Sixty-nine new figures have been added, and a detailed comprehensive index ends the volume. Short bibliographies are appended to each chapter. The book is recommended as an authoritative reference work.

Diabetic Care in Pictures. Simplified statements with illustrations prepared for the use of the patient. By Helen Rosenthal, B.S., associate dietitian in the Food Clinic, Boston Dispensary and assistant in medicine, Tufts College Medical School; Frances Stern, M.A. (honorary), chief of the Food Clinic, Boston Dispensary, instructor of medicine, Tufts College Medical and Dental schools; special instructor in dietetics in social service, School of Social Work, Simmons College, and associate in nutrition, School of Home Economics, Simmons College; and Joseph Rosenthal, M.D., chief, Diabetic Clinic, assistant medical director and medical supervisor, Domestic Medical Service, Boston Dispensary, assistant professor of medicine, Tufts College Medical School, and associate physician, Joseph H. Pratt Diagnostic Hospital. 8°, cloth, 150 pp., with 137 illustrations. Philadelphia: J. B. Lippincott Company, 1946. \$2.00.

This manual is written in simple language and is adequately illustrated with photographs, charts and drawings. It is designed for the use of the diabetic patient. The subjects covered include diet, insulin and its reaction, acidosis and

coma, blood and urine tests, skin injuries, and personal and special hygiene, especially of the hands and feet. A short chapter on personal and social factors concludes the text. The ring type of binding employed is not suitable for hard usage in the home. This manual should prove valuable to persons with diabetes when used in conjunction with a physician's instructions.

Famine, Rationing and Food Policy in Cochín. By K. G. Sivaswamy. With medical surveys by Lt. Col. T. S. Shastri and Dr. J. A. Bhat. 8°, paper, 35 pp., illustrated. Royapettah, Madras: Servindia Kerala Relief Centre, 1946. Rs. 3.

In this pamphlet the economics and control of food in Cochín State are discussed. The author advocates a short-range program to arrest deterioration in the health of children and expectant and nursing mothers. Special attention is called to malnutrition and to inadequate diets. The appendices are devoted to statistics.

Rare Diseases and Some Debatable Subjects. By F. Parkes Weber, M.D., F.R.C.P., physician to the German Hospital, London. 8°, cloth, 174 pp., illustrated. London: Staples Press, Limited, 1946. 15 sh.

This collection of thirty-one short articles, mostly reprinted from medical periodicals, covers the whole field of clinical medicine. Among the subjects briefly discussed are dysplasias and dystrophies of the subcutaneous tissue, unusual forms of rheumatoid arthritis, vascular disorders, flushing and blushing, calcinosis, endocrinologic conditions, diseases of the liver and biliary ducts and disorders of the nervous system. There are also short chapters on overnutrition, on the influence of Freud, on euthanasia and on the urge to collect. The volume ends with a short series of epigrams and poems.

NOTICES

MASSACHUSETTS CENTRAL HEALTH COUNCIL

The annual luncheon meeting of the Massachusetts Central Health Council will be held on Thursday, May 1, at noon at the Women's Educational and Industrial Union, 264 Boylston Street, Boston. The subject for discussion will be "Local Health Councils." Several active councils will report briefly on their work, after which Dr. Elmer S. Bagnall, former president of the Massachusetts Medical Society, and Dr. Hugh R. Leavell, professor of public-health administration, Harvard School of Public Health, will open the discussion.

Physicians and other persons interested in any aspect of public health are invited to attend. The lunch will cost \$1.50. Persons who wish to be present should notify the secretary, Mr. Arthur J. Strawson, 1148 Little Building, Boston (HAncock 5480).

TUBERCULOSIS INSTITUTE

A better understanding of the tuberculous patient, with an emphasis on the psychiatric approach to this problem, will be the topic of an all-day institute to be held on May 9 at the Hotel Bradford, Boston. The program has been arranged particularly by the Massachusetts Conference of Tuberculosis Secretaries, an organization composed of professional workers on the staffs of the Massachusetts Tuberculosis League and its affiliated associations. Several other agencies, including the Massachusetts Medical Society, are also sponsoring the meeting.

The program will include a morning session, a luncheon meeting and a panel discussion in the afternoon. Outstanding authorities in the field of tuberculosis and psychiatry have been invited to participate. Inquiries regarding the institute should be addressed to Miss Mabel M. Brown, Program Committee, Cambridge Tuberculosis and Health Association, 689 Massachusetts Avenue, Cambridge.

PHI DELTA EPSILON LECTURE

The first annual Phi Delta Epsilon Lecture at the Hahnemann Medical College, Philadelphia, will be delivered by Dr. Frank H. Lahey, of Boston, on Monday, May 12. Dr. Lahey will speak on the subject "Surgery of the Stomach Duodenum and Jejunum."

HARVARD MEDICAL ALUMNI ASSOCIATION

The annual meeting and dinner of the Harvard Medical Alumni Association will be held at the Hotel Clarendon, Atlantic City, New Jersey, on Wednesday, June 11, at 7:30 p.m., during the sessions of the one-hundredth anniversary meeting of the American Medical Association.

TUFTS MEDICAL ALUMNI DINNER

During the celebration of the one hundredth anniversary of the American Medical Association in Atlantic City, the Tufts Medical Alumni Association will hold a dinner on Wednesday, June 11, at 6:30 p.m., at the Ritz-Carlton Hotel. All alumni and their guests are invited to attend. There will be speakers from Boston and other cities who will discuss the medical school and its activities.

RESIDENCIES IN PSYCHIATRY

Psychiatric residencies have been established at the Pratt Diagnostic Hospital, 30 Bennet Street, Boston, and will be one year in duration. The patients will consist largely of those with neuroses or with emotional or personal complications of disease. There will also be a limited number of patients with psychosis. The residents' work will consist of the diagnosis and workup of the case and the handling and treatment of the patient. About 1500 inpatient and 500 outpatient cases are seen annually.

Applications will be considered from men of good standing of a Class A medical school who have had either a medical or a neurologic internship as a minimum. Applications should be forwarded to Mr. Richard T. Viguers, Administrator.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MAY 1

THURSDAY, MAY 1

*12:00 m. Massachusetts Central Health Council Women's Educational and Industrial Union, Boston

FRIDAY, MAY 2

*10:00 a.m.-12:00 m. Medical Staff Rounds' Peter Bent Brigham Hospital

MONDAY, MAY 5

*12:15-1:15 p.m. Clinicopathological Conference Peter Bent Brigham Hospital

TUESDAY, MAY 6

*12:15-1:15 p.m. Clinicoradiological Conference Peter Bent Brigham Hospital

WEDNESDAY, MAY 7

*11:00 a.m.-12:00 m. Medical Clinic Amphitheater Children's Hospital

*12:00 m. Clinicopathological Conference (Children's Hospital) Amphitheater, Peter Bent Brigham Hospital

*2:00-3:00 p.m. Combined Clinic by the Medical Surgical and Orthopedic Services Amphitheater Children's Hospital

*Open to the medical profession

APRIL 26-MAY 4 Industrial Health Meetings Page 456 issue of March 20

APRIL 28-MAY 2 American College of Physicians Page 206 issue of August 8

MAY 1 Massachusetts Central Health Council Notice above

MAY 6 Greater Boston Medical Society Page 610, issue of April 17

MAY 8 Cerebral Hemorrhage Dr. Raymond Adams Pentucket Association of Physicians 8:30 p.m. Haverhill

MAY 9 Boston University School of Medicine Alumni Association Page 554, issue of April 10

MAY 9 Tuberculosis Institute Notice above

MAY 12 Phi Delta Epsilon Lecture Notice above

MAY 19-22 Massachusetts Medical Society Annual Meeting Hotel Statler, Boston

MAY 20-22 Massachusetts Physicians Art Association Page 340 issue of February 27

JUNE 5-8 American College of Chest Physicians Page 418 issue of March 13

JUNE 7 AND 8 American Society for the Study of Sterility Page 304 issue of February 20

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The New England Journal of Medicine

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Volume 236

MAY 1, 1947

Number 18

HUMAN LABORATORY INFECTION WITH VENEZUELAN EQUINE ENCEPHALOMYELITIS VIRUS*

Report of Four Cases

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PEARL RIVER, NEW YORK

THE occurrence of human cases of encephalomyelitis due to laboratory infection with Venezuelan equine encephalomyelitis virus was reported for the first time by Casals et al.¹ and by Lennette and Koprowski² in 1943. The course of the disease described by these authors varied from patient to patient, mild, almost ambulatory cases paralleled severer ones in which involvement of the central nervous system was manifest.

Two fatal cases with subsequent isolation of Venezuelan equine virus from the brain tissue were subsequently recorded.^{3,4} One of these cases preceded³ whereas the other occurred during⁴ an epidemic caused by the same virus among horses and mules in Trinidad, British West Indies.^{4,5}

Finally, Gallia and Kubes,⁶ examining the serums of laboratory workers at the Institute of Veterinary Research in Caracas, Venezuela, found high titers of neutralizing antibody against Venezuelan equine encephalomyelitis virus in 10 of 16 cases. In only 1 of the 10 subjects involved, however, were there clinical manifestations that could have been attributed to the virus infection.

The purpose of the present report is to describe 4 human cases of laboratory infection with the Venezuelan virus, in 2 of which, prior to infection, there had been no known direct contact with the virus. The clinical course of the infection varied from a relatively mild disease to a severe infection that gave cause for alarm.

EPIDEMIOLOGY

In the second half of January, 1945, a strain of Venezuelan equine encephalomyelitis virus was obtained from Dr. J. Casals, of the Rockefeller Institute for Medical Research, New York. The virus was inoculated into mice on January 22. On

January 25 the mice became sick and were sacrificed. The brains of the animals were removed, and an infectious brain suspension was distributed into ampules and lyophilized.

These experiments were carried out in an animal house, situated approximately 300 yards from the main laboratory, where all subsequent work with the virus was performed. On January 30 a tube of the lyophilized preparation was rehydrated, and the contents inoculated into a lot of fifty eggs containing developing chick embryos. The majority of the embryos were found to be moribund on the afternoon of January 31, when the embryos were harvested. The infected embryos were homogenized in a Waring blender and then immediately formalized to prepare a vaccine.

The inoculation and harvesting of the embryos was done in a small sterile room to which only the personnel working directly with the Venezuelan virus, consisting of a physician and two assistant technicians, had access.

The eggs from which the infected embryos had been removed were deposited in a pail to which a 5 per cent solution of lysol was immediately added. All glassware and instruments used in the work were placed in a covered enamelware container. Late in the afternoon of January 31 the pail and the enamelware container were removed to the adjacent main laboratory, where three other persons, not connected in any way with the experiments on the Venezuelan virus, were working. On February 1 the pail was removed by a laboratory janitor to a disposal place, and the enamelware pan, containing the infected glassware and instruments, was filled with water and brought to the boiling point and then removed to the laboratory kitchen by the two assistant technicians who, on that day, did not have any further contact with the virus. The physician who was in charge of the work was absent from the laboratory on February 1.

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The first two human infections (Cases 1 and 2) appeared on February 2 in the assistant technicians who had been closely connected with the work on the virus. The third (Case 3) appeared in the evening of the same day in a biochemist who had not worked with the virus but who had been present in the main laboratory when the work with the virus was performed in the adjacent sterile room. Finally, the fourth infection (Case 4) appeared during the night of February 2 in a serologist who had not even worked in the main laboratory room, adjacent to the sterile room in which the studies on Venezuelan equine encephalomyelitis were carried on. On one or two occasions daily, however, he had passed the main laboratory room to and from his laboratory. The almost simultaneous occurrence of infection in the 4 patients indicated the presence of a common source of infection. This was strongly suspected to be connected with the work done on the Venezuelan virus, since the virus was known to be highly infectious² and since the only person who worked directly with the virus and did not show any symptoms of disease was the physician in charge, who was known to be immune to Venezuelan virus as a result of a previous infection.²

CASE REPORTS

CASE 1 D I, a 24-year-old assistant laboratory technician, reported that she awoke on February 2 with a general feeling of malaise.* A throbbing frontal headache set in, and she remained in bed the entire day. In the afternoon she developed generalized muscular pains, felt weak, had no appetite and spent a sleepless night in spite of the ingestion of "sleeping pills."

Her condition remained essentially the same during the next day except that, in addition, she complained of pharyngeal irritation. A physician discovered no unusual physical findings and diagnosed the illness as "grippe," although the patient did her best to convince him that she had "Japanese encephalitis." She ascribed this notion to the fact that shortly before the onset of the illness she had been vaccinated with a formalin-inactivated preparation of mouse-brain suspension infected with Japanese B encephalitis virus. The physician prescribed sedatives and sulfadiazine.

On February 4 the patient felt "somewhat better." The headache, pharyngeal irritation and muscular pains persisted but were of diminished intensity. She still had no appetite and complained of drowsiness, although she stated that she was able to sleep only after taking large doses of "sleeping pills."

On February 5 the patient felt much better. The pharyngeal irritation, muscular pains and drowsiness disappeared, but a slight frontal headache remained. She asserted that she still felt weak and had no appetite. It is assumed, however, that convalescence began on that date (February 5), for 3 days later the patient was symptom free except for weakness. She reported back to work on February 14, stating that she had been too weak to make the trip to the laboratory before that date.

CASE 2 D J S, a 22-year-old assistant laboratory technician, was well until about 10 a.m. on February 2, when she suddenly developed malaise and generalized body aches. The face was hot and flushed, and the whole body felt warm. The temperature was 101.1°F. After a specimen of the blood had been taken, the patient left the laboratory and went home to bed. She felt extremely drowsy and developed an almost unbearable headache localized between the eyes. Generalized body aches persisted, and she developed mild photophobia.

She had no appetite but slept the entire night. The next day her condition remained unchanged, and a physician made the diagnosis of "grippe" and prescribed sedatives and sulfadiazine. The appetite remained poor, and the patient was quite weak. On February 4 she awoke feeling much better since all the symptoms, except the frontal headache, had diminished. On the following day she suffered a slight relapse and again felt feverish, the headache became more accentuated and the feeling of malaise returned. The symptoms subsided in the evening, however, and she spent a restful night. On February 6 she spent an afebrile day and had few complaints. She still felt weak, but her appetite was normal.

Recovery was uneventful, and the patient reported back to work on February 15.

CASE 3 D W McK, a 34-year-old biochemist, developed the illness on February 2, when at about 7 p.m. he suddenly noticed that he felt more tired than usual. During dinner he was conscious of a "lightheaded feeling," and a throbbing frontal headache soon appeared that was accompanied by a bothersome pharyngeal irritation. The headache became progressively worse, and at about 10 o'clock he started to have paroxysms of chills that lasted almost uninterrupted for 2 hours. He had profound mental depression and during the night was feverish and delirious, at 3 a.m. he vomited partially digested food stained with bile. On the following day his condition remained unchanged except that he complained of muscular pains chiefly localized in the calf muscles. He was seen by a physician, who prescribed penicillin by mouth and a cough syrup containing codeine. In the afternoon a specimen of blood and a throat washing were taken. The patient slept during the 2nd night, and the temperature declined in the afternoon of February 4. The headache became less intense, but muscle and joint pains and pharyngeal irritation persisted.

On February 5 a macular rash appeared over the abdomen, inguinal folds and buttocks. The rash disappeared on the next day, and it was subsequently discovered that the patient was apparently sensitive to codeine, the administration of which had presumably caused the rash. The intensity of the systemic symptoms declined gradually throughout February 5 and 6.

On February 7 he awoke without the previous symptoms but developed complete anosmia and agusia that persisted for 2 weeks and disappeared spontaneously.

On February 12 the patient resumed work at the laboratory.

CASE 4 † D W, a 36-year-old serologist, awoke on February 3 at about 4 a.m. with a shaking chill. The temperature was 102.9°F. A throbbing ache appeared over the occiput and in both eyes, and he experienced generalized muscular and joint pains. During the following 8 hours the patient had three more shaking chills, and the headache became severe and predominantly frontal and retro-orbital. The muscle pains became localized in the lumbar region. Since the patient had been working with material containing living *Rickettsia orientalis* during the period immediately preceding the illness, the possibility of scrub typhus infection was suspected, and he was hospitalized about 7 hours after the onset of symptoms.

Physical examination disclosed a well developed and well nourished man who appeared acutely ill. The temperature was 103.5°F, and the pulse rate 106. No abnormalities except tachycardia and a fairly loud blowing systolic murmur between the sternum and the apex of the heart were discovered. The total white-cell count was 10,600. A blood sample was obtained from the patient for bacterial culture and inoculation of animals.

At 5 p.m. the patient was still acutely ill and uncomfortable, with a severe throbbing headache, photophobia and profuse sweating. The temperature was 101.3°F, and the pulse rate 110. In spite of the fact that the patient had no rash, his condition was tentatively diagnosed as scrub typhus fever, and medication with methylene blue† — 20 gm. per day — was started at 8:15 p.m. One hour after taking the first 0.5-gm.

†Reported through the courtesy of Dr. Walsh McDermott of the Department of Medicine, Cornell University Medical College.

†Medication with methylene blue was based on the work of Petersen and Fox⁷ who observed survival of mice infected with scrub typhus following treatment with the agent.

*The description of this case presented certain difficulties because the patient was highly susceptible to suggestion.

case, the patient became nauseated and vomited some of the drug.

On February 4 the patient was definitely improved, although he was still uncomfortable with a headache, muscular pains and pain in the calves. The temperature at 9 a m was 99.5°F, and the pulse rate 102 per minute, the total white-cell count was 5500. After another 0.5-gm dose of methylene blue, the patient vomited, and the dosage was cut down to 0.25 gm every 3 hours. On this dosage he was still nauseated but did not vomit. He also received two doses of 0.3 gm of codeine sulfate. At 9 p m the temperature was 101.1°F.

On the following day the patient continued to improve. The temperature at 8 a m was 99.1°F. The headache had virtually disappeared, and the muscular pains and backache were of diminished intensity. Methylene blue was continued (0.25 gm every 3 hours), and nausea persisted.

On February 6 the patient's condition had further improved. The temperature was 99.9°F at 7 a m. Since the results of the inoculation of the patient's blood into animals indicated that the diagnosis of scrub typhus fever was not probable, the administration of methylene blue was discontinued.

On the morning of February 7 the temperature was still 99.9°F. Examination of the urine revealed red cells and 15 to 20 white cells per high-power field in the sediment. This was considered to indicate cystitis or urethritis, possibly provoked by the ingestion of methylene blue.

During the next few days the patient's condition, except for a slight headache, remained essentially normal. The temperature averaged 100.4°F, and the white-cell count between 6400 and 8000.

On February 14 the severe headache recurred during the afternoon. The white-cell count was 14,000, but the patient was still almost afebrile. Lumbar puncture yielded a crystal-clear fluid. No bacterial organism was cultivated from the spinal fluid, and a complete laboratory analysis yielded practically negative results. Red cells were still present in the urine, although in diminished numbers. During the next day the patient's condition was practically normal except for a feeling of weakness and dizziness on standing. These symptoms gradually disappeared, and the patient was discharged from the hospital on February 23.

After discharge, recovery was uneventful, and the patient reported back to work on March 1.

ISOLATION OF THE VIRUS

No blood was obtained from the patient in Case 1 during the illness. Blood was obtained on the first day of the illnesses in Cases 2 and 4, and on the second day in Case 3.

Each specimen of serum was injected intracerebrally in amounts of 0.03 cc into 6 albino Swiss mice twenty-one to twenty-eight days of age. All the inoculated mice were either sick or dead forty-eight hours after inoculation, and the survivors were sacrificed. The brains were removed, and a suspension was prepared according to a technic described elsewhere.² The bacteriologically sterile suspensions were then distributed in ampules, lyophilized and stored for five months at 4°C.

In addition, a throat washing obtained from the patient in Case 3 on the second day of the illness was inoculated intranasally in 0.05-cc amounts into 10 mice. The majority of the mice were sick on the sixth day after inoculation. The sick mice were sacrificed, and since the lungs were normal on gross examination, the brains were removed and dealt with as mentioned above.

Five months later an ampule of each of the four strains was rehydrated with physiologic saline solution, and the contents were inoculated intracerebrally into mice. Forty-eight hours later, when the

mice were moribund, the brains were removed and a 10 per cent suspension by weight was prepared in a TenBroeck grinder. The suspensions were centrifuged for fifteen minutes at 1500 r p m in an International Size 1 machine equipped with an angle head, and the resulting supernatants were filtered through a Seitz EK pad, through which 20 cc of normal rabbit serum and saline solution had previously been passed.

Serial tenfold dilutions of the four filtrates were made and tested for infectivity by the inoculation of albino Swiss mice, eighty to one hundred and twenty days old, with 0.03 cc each by the intracerebral and intraperitoneal routes, respectively.

Rabbits, 1.4 to 2.3 kilograms in weight, were also injected with the filtrates, 2 animals being used for each of the 10⁻⁵ and 10⁻⁶ dilutions. All rabbits were injected by the intra-abdominal route with 1.0 cc of the material.

The LD₅₀* titers of the four filtrates in mice varied between 10^{-5.5} and 10^{-3.5} by the intracerebral route and between 10^{-7.0} and 10^{-8.2} by the intraperitoneal route (Table 1). Thus, with the exception of Case 2, the intraperitoneal LD₅₀ titer was only one log lower than the intracerebral. These results indicated that the causative agent readily passed the Seitz filter, and that it was of high invasive power for adult mice inoculated by the parenteral route.

The results of inoculation in rabbits (Fig. 1) further confirmed the highly invasive power of this filterable pathogen. All the animals reacted with fever and succumbed after a fulminant course of disease, with manifestations of marked cerebral involvement such as tremors, ataxia, clonic convulsions and paralysis, the rabbits died seventy-two to two hundred and sixteen hours after inoculation.

After the experiments had been concluded it became clear that the causative agent was a virus of neurotropic properties and of lethal action for adult mice (eighty to one hundred and twenty days old) and for rabbits, even when inoculated in a high dilution by the parenteral route. The Venezuelan equine encephalomyelitis virus seemed to correspond most closely to these characteristic properties,² and an attempt was therefore made for further identification.

IDENTIFICATION OF THE VIRUS

Neutralization tests were performed with the four infectious agents recovered from Cases 2, 3 and 4 and with serum from a rabbit that was known to be immune to Venezuelan equine encephalomyelitis. Normal and immune serums of the same animal were used in each case. The same rabbit serums had been used in previous experiments for identification of human strains of Venezuelan virus.² The technic of neutralization test followed exactly that previously described,² except that adult mice eighty to one

*LD₅₀ represents the dilution of virus of which 0.03 cc. will kill 50 per cent of the mice within the test period.

hundred and twenty days of age, inoculated by the intraperitoneal route with 0.05 cc of the respective virus dilution, were used throughout the study. Five mice were injected with each dilution. The test, with the agent recovered from Case 4, was done in duplicate, the second test being performed by Dr. J. Casals, of the Rockefeller Institute for

toms. Blood was obtained from the patient in Case 4 on the thirty-fourth day after the onset of symptoms. These convalescent-phase serums were compared for neutralizing capacity with acute phase blood specimens obtained from the patient in Cases 2, 3 and 4 on the first and second days of illness. To eliminate the presence of living virus

TABLE 1 *Pathogenicity for Adult Mice of the Filterable Agent*

CASE No	SOURCE OF VIRUS	ROUTE OF INOCULATION	MORTALITY RATIO WITH VIRUS DILUTIONS						LD ₅₀ TITER OF VIRUS
			10 ⁻⁵	10 ⁻⁶	10 ⁻⁷	10 ⁻⁸	10 ⁻⁹	10 ⁻¹⁰	
2	Serum	Intraperitoneal	5/5	3/4	2/5	2/5	0/5	0/5	10 ^{-7.0}
		Intracerebral	—	—	5/5	5/5	5/5	0/5	10 ^{-8.5}
3	Throat washing	Intraperitoneal	5/5	5/5	4/5	1/5	0/5	0/5	10 ^{-7.5}
		Intracerebral	—	—	4/4	5/5	1/5	0/5	10 ^{-8.5}
	Serum	Intraperitoneal	5/5	5/5	5/5	3/5	0/5	0/5	10 ^{-8.2}
		Intracerebral	—	—	5/5	5/5	1/5	2/5	10 ^{-8.9}
4	Serum	Intraperitoneal	5/5	4/4	3/4	1/5	1/4	0/5	10 ^{-7.4}
		Intracerebral	—	—	5/5	5/5	1/4	0/5	10 ^{-7.7}

Medical Research, on guinea pigs inoculated by the intra-abdominal route with mixtures of virus and immune serum.

Table 2 shows the results of the test. The immune rabbit serum that had previously been tested for specificity² showed a high neutralizing capacity for all four human strains. The guinea-pig test con-

from the acute-phase serums, the samples were submitted to inactivation for two hours at 56°C and were used only after a safety test, performed in mice observed for twenty-one days, had indicated the absence of living viruses from the specimen.

A strain of Venezuelan equine encephalomyelitis virus, obtained from Dr. Casals, was used as source

TABLE 2 *Results of Neutralization Tests with Human Viruses and Venezuelan Equine Encephalomyelitis Immune Serums in Adult Mice Inoculated by the Intra-abdominal Route*

CASE No	SOURCE OF VIRUS	RABBIT SERUM	MORTALITY RATIO WITH SERUM AND VIRUS DILUTIONS										LD ₅₀ TITER OF VIRUS	LD ₅₀ DOSES OF VIRUS NEUTRALIZED
			10 ⁻¹	10 ⁻²	10 ⁻³	10 ⁻⁴	10 ⁻⁵	10 ⁻⁶	10 ⁻⁷	10 ⁻⁸	10 ⁻⁹	10 ⁻¹⁰		
2	Serum	Normal	—	—	—	—	—	—	4/4	0/5	0/5	0/5	10 ^{-7.5}	316,000
		Immune	4/5	3/5	0/5	0/4	0/5	0/5	0/5	—	—	—	10 ^{-2.4}	
3	Throat washing	Normal	—	—	—	—	—	4/5	4/5	2/5	0/5	0/5	10 ^{-7.4}	501,200
		Immune	4/5	2/5	0/5	0/5	0/5	0/5	—	—	—	—	10 ^{-1.7}	
	Serum	Normal	—	—	—	—	—	5/5	4/5	3/5	1/5	0/5	10 ^{-8.2}	1,000,000
		Immune	4/5	3/5	1/5	0/5	0/4	0/5	—	—	—	—	12 ^{-2.2}	
4	Serum	Normal	—	—	—	—	—	5/5	5/5	4/5	0/5	0/5	10 ^{-8.4}	25,120,000
		Immune	0/5	0/5	2/5	0/5	0/5	0/5	—	—	—	—	10 ^{-1.0}	
	Serum	Normal*	—	—	4/4	4/4	4/4	4/4	4/4	4/4	—	—	10 ^{-8.2}	1,000,000
		Immune*	—	0/4	0/4	0/4	0/4	0/4	—	—	—	—	10 ^{-2.8}	

*Test performed with normal and immune guinea pig serums by Dr. J. Casals, of the Rockefeller Institute for Medical Research. Guinea pigs instead of mice were used in the neutralization test.

firmed these findings, from which it may be deduced that the infectious agent was identical with the virus of Venezuelan equine encephalomyelitis virus.

APPEARANCE OF NEUTRALIZING ANTIBODIES

Blood was obtained from the patients in Cases 1, 2 and 3 at intervals of nineteen, nineteen and eighteen days, respectively, after the onset of symp-

in the neutralization test. The procedure of the test followed that described above.

The results of the test are presented in Table 3. The titer of the virus in the presence of acute-phase serums ranged from 10^{-7.6} to 10^{-8.2}. In the presence of convalescent serums the LD₅₀ titer of the virus was 10^{-1.0} or lower in Cases 2, 3 and 4 and 10^{-1.6} in Case 1. Thus, even in Case 1, in which no serum

sample obtained during the acute phase of the disease was available for comparison, it may safely be assumed that the patient on February 20, was immune to the Venezuelan equine encephalomyelitis virus

The development of antibodies in patients during their convalescence in concentrations neutralizing

this laboratory In 1938 the V-1938^s strain of the virus was brought, for the first time, from Venezuela to the Lederle Laboratories and worked with for a period of about two years.⁹ Although no signs of infection were observed among persons working with the virus at that time, it seemed to be of interest to examine the serums of those connected

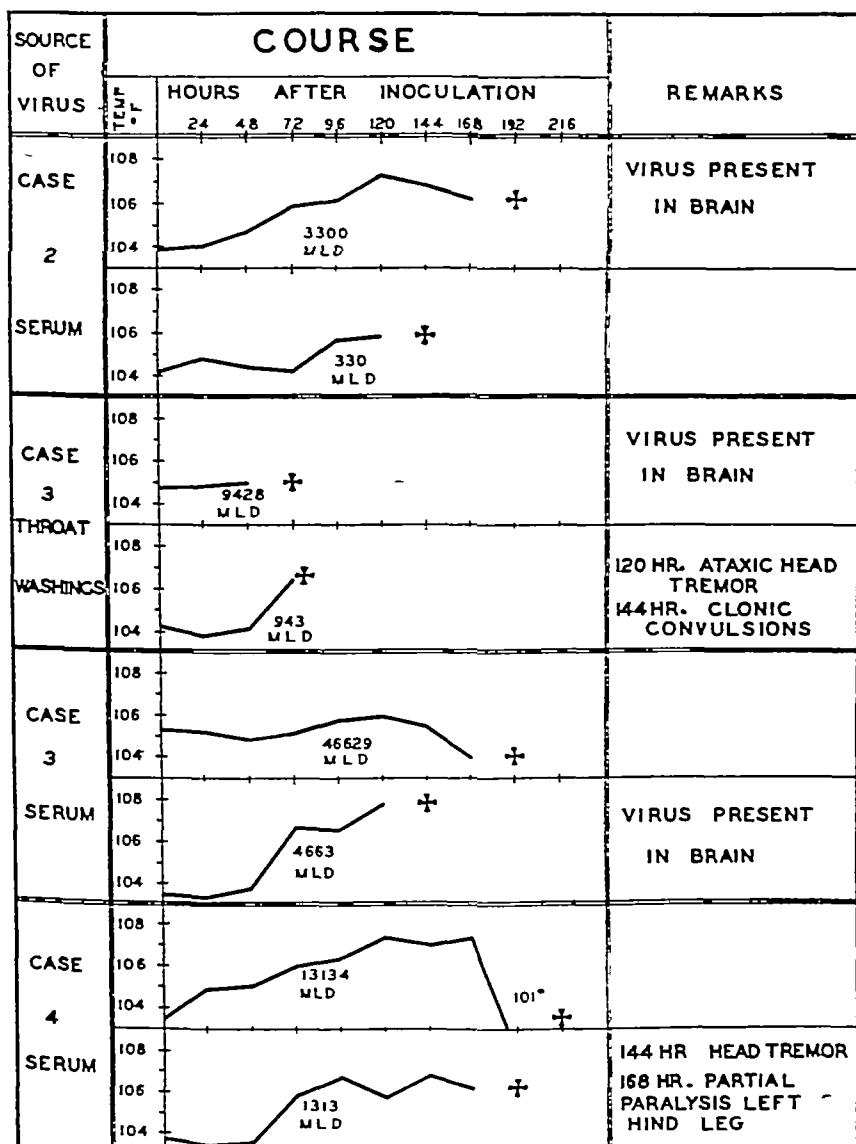


FIGURE 1

130,000 or more minimal lethal doses of the Venezuelan virus is additional evidence that the human infections were due to this agent

RESULTS OF NEUTRALIZATION TESTS IN PERSONS PREVIOUSLY EXPOSED TO VIRUS

The present infection was not the first occasion on which the Venezuelan virus has been brought to

with the work for the presence of neutralizing antibodies directed against the Venezuelan virus. Blood was obtained from 3 of these persons (W T, J M and J K) who were still working in the Laboratory and from another (H R C), who had worked on the isolation of the virus from Case 4 of the present series. Blood was also obtained from 2 persons (M P and J B) who had been working in the

same room as the patient in Case 3 and who, although not in direct contact with the virus, had become sick with symptoms consisting of fever, headache and muscular pains almost simultaneously with the positively diagnosed cases described above. As a positive control of the test, a serum sample was obtained from one of us (H K) who had had

been infected or because the amount of neutralizing antibodies in the blood had decreased below a detectable level.

DISCUSSION

As mentioned above the Venezuelan virus was handled in this laboratory on only two occasions:

TABLE 3 Results of Neutralization Test with Venezuelan Equine Encephalomyelitis Virus and Human Serums in Adult Mice Inoculated by the Intra-abdominal Route

CASE No	INTERVAL AFTER INFECTION	MORTALITY RATIO WITH SERUM AND VIRUS DILUTIONS										LD ₅₀ TITER OF VIRUS	LD ₅₀ DOSES OF VIRUS NEUTRALIZED
		10 ⁻¹	10 ⁻²	10 ⁻³	10 ⁻⁴	10 ⁻⁵	10 ⁻⁶	10 ⁻⁷	10 ⁻⁸	10 ⁻⁹	10 ⁻¹⁰		
1	19 days	2.5	3.5	1.5	0.5	0.5	0.5	—	—	—	—	10 ^{-1.5}	?
2	19 days	0.5	0.5	2.5	1.5	0.5	0.5	5.5	2.5	0.5	0.5	10 ^{-7.5} 10 ^{-1.0}	7,943,000
3	18 days	1.5	0.5	0.5	0.5	0.5	0.5	4.5	1.5	1.5	0.5	10 ^{-7.5} 10 ^{-1.0}	3,981,000
4	34 days	2.4	0.4	0.5	0.5	0.5	0.5	5.5	5.5	0.5	0.5	10 ^{-8.5} 10 ^{-1.0}	15,850,000

Venezuelan equine encephalomyelitis in July, 1943.²

The technic of the test was the same as that described above.

The results are shown in Table 4. It will be observed that the titer of the virus, in the presence of immune serum of H K, was lower than 10^{-3.0} whereas in the presence of serums obtained from other persons, the titer ranged from 10^{-7.0} to 10^{-8.5}.

before it became the cause of human infections. On the first occasion, the work was carried out in the animal house to which 2 patients (Cases 3 and 4) did not have access at that time. Thus, it seems probable that these patients, as well as the other 2, became infected when the virus was handled in the main laboratory—that is, sometime between January 30, when a tube of lyophilized

TABLE 4 Results of Neutralization Test with Venezuelan Equine Encephalomyelitis Virus and Serums of Persons Who Had Contact with Virus

SUBJECT	DATE OF WITHDRAWAL OF BLOOD	TYPE OF WORK	ILLNESS	MORTALITY RATIO OF ADULT MICE WITH SERUM AND VIRUS DILUTIONS								LD ₅₀ TITER OF VIRUS
				10 ⁻³	10 ⁻⁴	10 ⁻⁵	10 ⁻⁶	10 ⁻⁷	10 ⁻⁸	10 ⁻⁹	10 ⁻¹⁰	
M P	2/21/45	Worked in the same room as Cases 1, 2 and 3	Yes	5.5	5.5	5.5	5.5	3.4	1.5	0.5	0.5	10 ^{-7.5}
J B	2/19/45	Worked in the same room as Cases 1, 2 and 3	Yes	5.5	5.5	5.5	5.5	2.5	1.4	0.5	0.5	10 ^{-7.5}
H R C	7/30/45	Laboratory work connected with isolation of virus from Case 4	No	—	—	—	5.5	5.5	3.5	2.5	0.5	10 ^{-8.5}
W T	5/24/45	Laboratory work connected with isolation of virus from Case 4	No	—	—	—	5.5	4.5	4.5	1.5	0.5	10 ^{-8.5}
J M	5/24/45	Animal caretaker	No	4.4	5.5	5.5	5.5	3.5	0.5	0.5	0.5	10 ^{-7.5}
J K	5/24/45	Animal caretaker	No	5.5	5.5	5.5	5.5	3.5	1.5	1.5	0.5	10 ^{-7.5}
H K	7/16/45	Positive control (laboratory infection in July 1943)	Yes	0.5	0.5	0.5	0.5	—	—	—	—	10 ^{-3.0}

— the usual titration end point of the virus in the absence of neutralizing antibodies.¹⁰

It may be assumed that the sickness of M P and J B was purely coincidental and that H R C, in spite of a recent direct contact with the Venezuelan virus, did not develop humoral immunity directed against this virus. Also, none of the persons (W T, J M and J K) who had worked with the virus in 1938–1940 showed demonstrable specific antibodies in the blood, either because they had not become in-

material was opened for inoculation of eggs, and February 1, when the eggshells and glassware and instruments used for harvesting of the chick embryos were disposed of. This would bring the incubation time of the disease in human beings up to three or four days, which is not improbable when compared with previous findings.²

The puzzling feature of the present report lies, however, in the fact that 2 patients became infected without having had any direct contact with

the virus. Moreover, as mentioned above, 1 of the patients (Case 4) did not even work in the same laboratory room in which work with the Venezuelan virus was carried on. Between January 30 and February 1 the work with Venezuelan virus was carried on in fertile eggs only, so that the latter must be considered the source of the infection in human beings. In view of what has been stated above, contact infection seemed to be out of the question, leaving inhalation of infectious material as the most probable route of infection. The type of infectious material that may have been inhaled by all 4 patients cannot be determined. One may speculate whether or not a small amount of the embryonic suspension spilled during blending, dried in the air

direct isolation of the virus, whereas the remaining 14 cases were diagnosed on the basis of the appearance of antibodies in the blood of the subjects. As further shown in Table 5, only 2 cases—those described by Randall and Mills³ and Gilyard⁴—occurred naturally, and they have been the only fatal cases reported so far. Of the remaining 24 cases, 14 were definitely due to laboratory infection, whereas the remaining 10 cases reported by Gallia and Kubes,⁶ were attributed to infections of probable laboratory origin, although since the respective subjects lived in Venezuela, there remains the possibility of an inapparent natural infection. In the entire series of 26 cases, besides the 2 fatal ones 2 patients showed symptoms that were regarded as severe, 13

TABLE 5 Summary of Human Cases of Infection Due to Venezuelan Equine Encephalomyelitis Virus

SERIES	TOTAL NO OF CASES	CASES WITHOUT SYMPTOMS	CASES WITH MILD SYMPTOMS	CASES WITH SEVERE SYMPTOMS	FATAL CASES	CASES WITH VIRUS ISOLATED FROM BLOOD	CASES WITH VIRUS ISOLATED FROM THROAT WASHING	CASES WITH VIRUS ISOLATED FROM BRAIN TISSUE	CASES WITH NEUTRALIZING ANTIBODIES IN CONVALESCENT SERUMS
Casals, Curnen and Thomas ¹	2		2			1			2
Lennette and Koprowski ²	8		7	1		6	1		8
Randall and Mills ³ and Gilyard ⁴	2				2			2	
Gallia and Kubes ⁶	10	9	1						10
Koprowski and Cox	4		3	1		—	1		4
Totals	26	9	13	2	2	10	3	2	24

and subsequently was inhaled by the patients, or whether some of the infected eggshells were crushed outside the containers and the resulting dust inhaled by the patients. Whatever the true fact may be, all speculations remain within broad limits of probability.

Nothing characteristic was observed about the course of the disease, which was similar in its signs and symptoms to that described by other authors.^{1,2} Fever, body aches and pains and a rather persistent and severe headache were common to all cases. Again, as described earlier,² 3 of the patients were believed to have had attacks of "grippe," the fourth being properly diagnosed only because of the patient's hospitalization.

Marked differences in the severity of the illness were also observed in the present series. Cases 1 and 2 were the least severe, whereas Case 4 was so severe as to give cause for alarm and, because of its severity and its period of remission, closely resembled Case 7 of the previous report.² In all the present cases, the course of the disease seemed to be severer than that described by Casals and his associates.¹

Since the cases described above increased the number of cases of human infections reported in the literature as due to Venezuelan virus to 26, all observations related to that infection in human beings were tabulated (Table 5). It may be observed that of the 26 cases reported, 12 cases were diagnosed by

had mild symptoms and 9 had no symptoms, although the serums neutralized the Venezuelan virus.

The facts that the only 2 fatal cases of Venezuelan encephalomyelitis occurred during an epizootic in Trinidad^{3,4} and that no known accidents were associated with the laboratory infections raise the question whether the relatively low infectiousness of the Venezuelan virus, observed in the latter cases, was related to the unnatural intranasal spread of the infection.* The human infections that occurred during the epizootic were, in all probability, caused by the bite of an infected mosquito, and the intracapillary route of infection may have resulted in a much more fulminant spread of the infection, ending in the death of the patients. On the other hand, the lack of reports of fatal human cases occurring among the inhabitants of Venezuela residing in regions where the virus is enzootic must be considered.

The invasive power of Venezuelan equine encephalomyelitis virus for man is high and yet its virulence for man apparently remains comparatively low. The report of 2 fatal cases,⁴ however, and the ease with which the virus causes laboratory infection indicate the caution that must be exercised in working with the pathogen.

*Further evidence for the intranasal route of infection is suggested by the fact that all attempts to isolate the virus from throat washings (Table 5) were unsuccessful.

SUMMARY

Four cases of human infection with Venezuelan equine encephalomyelitis virus are reported. All were due to infection acquired in the laboratory. The virus was isolated from the circulating blood in 3 cases and from the throat washings in 1.

The diagnosis in these 3 cases as well as that in another was further substantiated by the appearance of specific neutralizing antibodies in the convalescent sera. These findings are discussed in the light of previous reports of human infection due to Venezuelan equine encephalomyelitis virus.

REFERENCES

1. Casals, J., Curnen, E. C., and Thomas, L. Venezuelan equine encephalomyelitis in man. *J. Exper. Med.* 77:521-530, 1943.
2. Lennette, E. H., and Koprowski, H. Human infection with Venezuelan equine encephalomyelitis virus: report on eight cases of infection acquired in laboratory. *J. A. M. A.* 123:1088-1095, 1943.
3. Randall, R., and Mills, J. W. Fatal encephalitis in man due to Venezuelan virus of equine encephalomyelitis in Trinidad. *Science* 79:225, 1944.
4. Gilyard, R. T. Clinical study of Venezuelan virus equine encephalomyelitis in Trinidad, B. W. I. *J. Am. Vet. M. A.* 106:267-277, 1945.
5. Kubes, V. Venezuelan type of equine encephalomyelitis virus in Trinidad. *Science* 99:41, 1944.
6. Galia, F., and Kubes, V. Neutralization of Venezuelan encephalomyelitis virus by human sera. *J. A. M. A.* 125:894-897, 1944.
7. Petersen, O. L., and Fox, J. P. Unpublished data.
8. Beck, C. E., and Wyckoff, R. W. G. Venezuelan equine encephalomyelitis. *Science* 88:530, 1938.
9. Wyckoff, R. W. G. Personal communication.
10. Lennette, E. H., and Koprowski, H. Neutralization tests with certain neurotropic viruses: comparison of sensitivity of extraneural and intracerebral routes of inoculation for detection of antibodies. *J. Immunol.* 49:375-385, 1944.

A SURVEY OF THE FIRST THREE MONTHS OF OPERATION OF A VETERANS ADMINISTRATION MENTAL-HYGIENE CLINIC

MORRIS H. ADLER, M.D.,* AND EDWARD M. L. BURCHARD, PH.D.†

BOSTON

SINCE the Mental Hygiene Clinic of the Veterans Administration began operation in Boston on March 18, 1946, a number of questions have been asked concerning the management of patients, the therapeutic goals, the types of patients who present themselves for treatment, the results and so forth. Although it is too early to permit an adequate reply to all the inquiries, a survey of the first three months' activities may clarify somewhat the work and aims of the clinic.

Since its opening the clinic has grown steadily both in patient load and in staff, although no attempt has been made to publicize its existence. At the time of writing further expansion has been stopped by lack of sufficient space for treatment rooms. At present the clinic is housed in a wing of the West Roxbury Veterans Hospital, which it fills to overflowing. On completion of more spacious quarters, an increase of more than twice the present number of patients treated will immediately be possible.

The staff consists of three full-time psychiatrists, four part-time psychiatric consultants, three full-time psychologists, five full-time psychiatric social workers and an office force of appropriate size. The move to larger quarters will permit the staff to be augmented immediately by four psychiatrists, a psychologist and three social workers. The eventual size of the staff can only be guessed at, since its further increase will depend entirely on the number of patients.

All patients referred to the clinic from any source are accepted on a trial basis without preliminary

screening. This is admittedly a generous admission policy, but in the initial stages of operation, it provides the only method of determining the types of patients that can be referred to a mental-hygiene clinic.

A broad base for referrals is being obtained, practically every community organization with which a veteran can be expected to make contact

TABLE 1 Patients Referred from Various Sources

Source	No. of Patients
Medical Outpatient Department, Veterans Administration	80
Social Service Department, Veterans Administration	54
Self	19
Harvard Guidance Clinic	16
West Roxbury Veterans Hospital	15
Outside physicians	15
Vocational Rehabilitation Division, Veterans Administration	7
Contact Division, Veterans Administration	4
Veterans Service Center	4
Jewish War Veterans	4
Bedford Veterans Hospital	2
Jewish Family Society	2
Outside hospitals	2
Psychiatric clinic	1
Red Cross	1
Civil Service Commission	1
Clergyman	1
Total	228

being represented. It is not surprising that by far the majority of patients are referred by some division of the Veterans Administration, but it is gratifying to note that of 228 patients, 19 were self-referred and 15 were referred by private physicians (Table 1).

Such an admission policy may be expected to give the clinic a high percentage of cases that will eventually prove to be therapeutic failures, but it is regarded as preferable at our stage of development

*Chief psychiatrist, Mental Hygiene Clinic, Veterans Administration, Boston.

†Chief psychologist, Mental Hygiene Clinic, Veterans Administration, Boston.

not to have any predetermined diagnostic or other criteria for refusing new applicants for psychiatric assistance. Several factors have dictated this decision. In the first place, it has been the experience of military psychiatrists that patients who in civilian practice would be considered poor material for treatment respond to psychotherapy. Secondly, it is believed that this clinic should take the lead in the development of new therapeutic devices and techniques of potential benefit in the management of patients hitherto considered resistant or unamenable to psychotherapy. A final reason for accepting all types of patients was that this practice keeps the clinic from becoming too one-sided and makes available a large and varied group of patients for teaching purposes.

So far as the legal aspects of this policy are concerned, eligibility for treatment has been established by Veterans Administration Circular No. 26, which, in effect, gives authority to the chief medical officer to determine whether or not a patient is eligible for psychiatric care. This permits immediate psychiatric care of veterans with service-connected disabilities, prior to completion of adjudication of their claims. A great advantage is that the policy avoids over-stress of symptoms in the hope of receiving treatment. The veteran is not made to believe that he must exhibit extreme and dramatic evidences of his illness to be treated. The clinic is thus enabled to do prophylactic work, instead of limiting itself to patients who had already suffered symptoms and had been hospitalized for them while in military service.

Despite this "open-door" policy, the great majority of patients fall into the general grouping of psychoneurotic disorders, only 15 of a total of 228 cases being classed as character and behavior disorders that are generally not amenable to treatment (Table 2). The high percentage of anxiety reactions agrees with the general experience of clinics and psychiatrists treating veterans.

Since our methods of managing patients are rather different from those in use in other mental-hygiene clinics, a short description of the procedures is of interest. On referral the patient is immediately given an appointment for the orientation class. Orientation sessions are held three times a week, and thus the initial contact with the clinic staff need never be delayed more than twenty-four hours. The orientation session, which is conducted by a psychologist and lasts an hour, is designed to answer the veteran's questions about clinic procedure and rules, methods of treatment, what he can expect to be done for him and what the clinic will expect from him. An attempt is also made in this first session to relieve some of the anxiety about the label "psychoneurosis" and to give the patient a rational and acceptable, although superficial, explanation for some of his symptoms.

After orientation, a complete history is obtained by a social worker—this usually requires two appointments and may extend to three or four in complicated or retarded cases. Such an extended period with the social worker has proved to be extremely valuable in the management of treatment. Not only can the treatment be speeded up because the psychiatrist has available a complete case history before he sees the patient but also the interview with the social worker serves as superficial psychotherapy in itself. The patient is forced into a biographical orientation that prepares him for more

TABLE 2 *Diagnoses*

DIAGNOSIS	NO. OF PATIENTS
Transient personality reaction	
Acute situational maladjustment	5
Psychoneurotic disorders	133
Anxiety reaction	91
Phobic reaction	2
Conversion reaction	12
Somatization reaction	2
Obsessive-compulsive reaction	2
Hypochondriacal reaction	14
Neurotic depressive reaction	2
Type undetermined	4
Character and behavior disorders	15
Immaturity reaction	7
Pathological behavior reaction	1
Pathological personality reaction	1
Type undetermined	1
Psychoses without known organic etiology	
Schizophrenic disorders	5
Psychoses with associated structural changes	3
Gastrointestinal disease	3
Diagnosis deferred	66
Total	228

searching therapy and frequently results in some reorientation toward his complaints before the initial contact with the psychiatrist. Furthermore, these interviews serve as a screening device for patients who are so unprepared for psychotherapy that they cannot even co-operate in the giving of biographical information at the conscious level.

After the history has been taken the patient sees a psychiatrist for a survey, at which time the tentative diagnosis, prognosis and program of treatment are determined.

Treatment may take the form of individual psychotherapy in addition to environmental manipulations, individual psychotherapy, individual psychotherapy with Pentothal Sodium as an adjuvant, hypnotherapy or group therapy. The type of therapy depends solely on the psychiatrist's judgment of what will benefit the patient most and the original program may be modified several times according to the patient's progress and responsiveness.

Since the great majority of patients respond reasonably well to individual psychotherapy with occasional sessions of Pentothal or hypnosis, this is the most frequently used method of treatment. Environmental manipulation is seldom utilized because of our deliberate policy of treating the patient

SUMMARY

Four cases of human infection with Venezuelan equine encephalomyelitis virus are reported. All were due to infection acquired in the laboratory. The virus was isolated from the circulating blood in 3 cases and from the throat washings in 1.

The diagnosis in these 3 cases as well as that in another was further substantiated by the appearance of specific neutralizing antibodies in the convalescent sera. These findings are discussed in the light of previous reports of human infection due to Venezuelan equine encephalomyelitis virus.

REFERENCES

1. Casals, J., Curnen, E. C., and Thomas, L. Venezuelan equine encephalomyelitis in man. *J. Exper. Med.* 77:521-530, 1943.
2. Lennette, E. H., and Koprowski, H. Human infection with Venezuelan equine encephalomyelitis virus: report on eight cases of infection acquired in laboratory. *J. A. M. A.* 123:1088-1093, 1943.
3. Randall, R., and Mills, J. W. Fatal encephalitis in man due to Venezuelan virus of equine encephalomyelitis in Trinidad. *Science* 99:225, 1944.
4. Gilyard, R. T. Clinical study of Venezuelan virus equine encephalomyelitis in Trinidad. *B. W. I. J. Am. Fa. M. A.* 106:267-277, 1945.
5. Kubers, V. Venezuelan type of equine encephalomyelitis virus in Trinidad. *Science* 99:41, 1944.
6. Gallia, F., and Kubers, V. Neutralization of Venezuelan encephalomyelitis virus by human sera. *J. A. M. A.* 125:894-897, 1944.
7. Petersen, O. L., and Fox, J. P. Unpublished data.
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Since the 28 per cent of patients who voluntarily ceased treatment before they were discharged in a sense constituted failures, this group was surveyed as intensively as the records permitted. In both diagnosis and source of referral the patients were not distinguished from the remainder treated. We were struck with the fact that 25 per cent of the group ceased reporting to the Clinic before they had made any contact with a psychiatrist and that

of the professional staff. Once a week a staff conference lasting an hour is held for psychiatrists and psychologists. At each meeting a member of the staff presents a case currently being treated. The dynamics behind the symptoms, the treatment program, the therapeutic technics and so forth are discussed and criticized by the entire staff. At these meetings, such considerations as problems of diagnostic nomenclature, sources and methods of

TABLE 4 *Disposition of Patients as of June 30, 1940*

DIAGNOSIS	PATIENTS DISCHARGED IMPROVED	PATIENTS DISCHARGED UP IMPROVED	PATIENTS FAILING TO KEEP APPOINT- MENTS	PATIENTS REFERRED TO VETERANS' ADMINISTRA- TION PROV- IDENCE RI	PATIENTS REFERRED TO "MASSACHU- SETTS" GENERAL HOSPITAL	PATIENTS REFERRED TO PSYCHIATRY CLINIC	PATIENTS ADMITTED TO HOSPITALS	PATIENTS BE- ING TREATED IN MENTAL HYGIENE UNIT
Transient personality reaction								2
Acute situational maladjustment	1							
Psychoneurotic disorder								
Anxiety reaction	7	1	27	1		3	1	51
Conversion reaction	1		2					6
Obsessive-compulsive reaction	1							2
Neurotic depressive reaction	1				1	1		4
Somatization reaction			1					4
Hypochondriacal reaction			1					1
Headache cause undetermined							1	
Phobic reaction								2
Type undetermined		1					1	1
Character and behavior disorder								
Immature reaction	1*	1†	1					1
Pathologic behavior reaction	1‡							1‡
Pathologic personality reaction			1					
Passive aggressive reaction								2
Aggressive reaction								2
Schizoid personality								1
Type undetermined			1					
Psychosis without known organic cause							2	2
Schizophrenic disorder			1				1	2
Epilepsy								
Gastrointestinal disease					1			
Diagnosis deferred or undetermined			24		1			41
Totals	15	5	67	1	3	4	6	127

*With symptomatic habit reaction

†With speech defect.

‡Inadequate depressed reaction

an additional 30 per cent failed to return after the first treatment interview. After the third hour of treatment the rate of attrition dropped off steeply, only 16 per cent of patients being lost. These findings strongly suggest that the patients ceased treatment because they were disappointed to find that the staff possessed no magical serums or formulas by means of which all their problems could be quickly and painlessly solved. The discovery that psychiatric treatment may be an uncomfortable process was probably too much for them, and they decided that to endure their symptoms would be less disturbing than to face them. It is to be expected that most of these men will return to the Clinic when their symptoms become severer, and a few have already done so. A survey is being conducted by the Social Service Department to discover the specific reason for discontinuance in these 67 cases.

Questions have been asked about the staff-training program and therapeutic goals. A definite educational program has been set up for all members

referral and the relative efficacy of various methods are brought to the attention of the staff.

For the social workers on the staff and those assigned to the Out-Patient Department two weekly seminars of an hour and a half each are held. Although primarily designed for social workers, the seminars may be attended by other staff members who are free at the time. In these seminars clinic plans, methods and procedures, basic psychological theory, the history of and the underlying dynamics involved in various anamnestic and therapeutic technics are discussed. Also, in each session, a complete case is discussed with emphasis on the dynamics and on the clues to dynamics that can be picked up during history taking.

A word about our therapeutic goals may be of interest. We are not deluding ourselves with the belief that a large proportion of patients will be cured in the relatively short period of treatment that has been set up as the maximum. Our experience, however, convinces us that an active therapeutic approach will enable us materially to improve the condition of a high percentage of

to as great an extent as possible exactly as if he were being treated by a psychiatrist in private practice. As a matter of policy, fifty hours of treatment has been set as the maximum, and it is our hope to render patients comfortable and symptom free in much less time.

Although it is too early for any definitive statistics on length of treatment, after three months' work, the Clinic has begun to build up a small but not inconsequential number of patients who have been treated for ten, fifteen and even twenty-eight hours (Table 3). Only a longer period will tell how

TABLE 3 *Hours of Treatment Given to All Patients on June 30, 1946*

HOURS OF TREATMENT	NO. OF PATIENTS
1	1
2	10
3	14
4	10
5	22
6	13
7	12
8	8
9	4
10	4
11	2
12	2
13	2
14	2
15	1
16	1
18	3
19	3
28	1

successful the treatment of such patients has been. These clinic "veterans" may have built up too great a dependence on the psychiatrist, although clinical judgment in these cases does not support this opinion. Rather, it seems that these men, who are being carried for longer periods, continue to come because they are gaining real—although limited—insight and increased skill in handling their interpersonal problems.

Group therapy is frankly being used as a socializing technic with patients diagnosed as character and behavior disorders who do not respond well to individual treatment. It is a psychiatric commonplace that psychopaths are resistant to uncovering and interpretation procedures because of a warped development that has resulted in improper or inadequate identification with parental authority images. We are giving such patients group therapy with the expectation of making therapeutic use of sibling relationships, which usually develop in such groups.

Groups of 6 to 8 patients are formed with a psychologist as group leader. Each group meets twice a week for an hour at a time for six weeks. The group leader is prepared with a set of twelve short lectures on topics designed to elicit group discussion of troublesome interpersonal problems. Although the lectures are educational in themselves and correct many frequent misapprehensions, they

are not considered treatment in themselves but are regarded as providing a stimulus for an atmosphere in which therapy can take place through group stimulation, development of sibling relationships and identification and recognition by each patient that his problem is not unique and individual but that he suffers from frequent symptoms with which his fellow sufferers can help him.

Each session is opened by a short presentation, lasting ten or fifteen minutes, of a triple-barreled topic designed to correct misapprehensions, elicit discussion and encourage emotional ventilation. Group discussion of the subject is invited and stimulated, the group leader serving as moderator but remaining unobtrusive so long as the patients continue to discuss any potentially therapeutic topic. At the end of the hour the leader summarizes the discussion and relates it to the specific problems of the men in the group.

Since the major purpose of group therapy is to develop sibling relationships, if a patient fails to keep an appointment for group therapy, one of the other patients who lives in his neighborhood endeavors to find the reason for his absence and to persuade him to return. It has been the policy of the Clinic not to have any member of the staff follow up patients who have ceased keeping their appointments. To do so would introduce an authoritarian element that, we believe, would disturb the type of emotional climate that we have been endeavoring to build up in the Clinic situation.

Our group-therapy program is considered effective in several ways, in addition to the building up of the sibling relationships and identifications mentioned above. Relaxation from tension, ventilation of hostility and aggression and considerable catharsis take place. Some patients obtain sufficient insight to become amenable to individual therapy after completion of a course of group therapy, others respond adequately to a simultaneous combination of group and individual therapy, attending group sessions twice a week and seeing a therapist once. Thus, group therapy is employed not only as treatment per se but also as a preparation for, and an adjuvant to, individual treatment.

The results obtained are demonstrated in Table 4, which summarizes according to diagnosis the disposition of all cases in our files on June 30, 1946. Fifteen per cent of the total were either discharged or referred to other agencies for indicated treatment, 28 per cent voluntarily ceased keeping appointments, and 55 per cent were being carried in treatment status. All diagnoses were represented to about the expected extent in each group, and the small number of discharges is to be expected from the short life of the Clinic. Our records show that the patients discharged as "improved" had been given an average of six and a half hours of treatment, and those discharged as "unimproved," five and a half hours.

On August 23, the carbon dioxide snow was administered. A week later the child returned because of failure of the lesions on the right forearm and left leg to respond. The lesion on the right forearm was 4 cm. long, red, raised and circinate (Fig. 1). Freezing therapy was again instituted. When the patient was seen last on September 13, the eruption on the left leg was still present.

CASE 2 R. C., a 5½-year-old boy, was first seen at the Department of Tropical Medicine, Harvard Medical School,

played in a pit in which cats were known to have defecated about thirty new, red, raised bumps were noted on the arms and legs. These lesions apparently appeared within 4 hours after the child became infected. As before, the macules were nonpruritic until the elongation of the burrows was apparent. Thereafter, the child was annoyed by itching. About August 1 the family left Georgia for a visit to the grandparents in New Hampshire. Owing to the severe itching, a physician was called to see the child. Two weeks later a differential count revealed an eosinophil count of 40 per cent. Because



FIGURE 1 Case 1

This photograph of the right forearm was taken on August 30. A central area of granulation tissue is present in the area that had received carbon dioxide-snow therapy one week previously. The burrow proximal to this had almost healed. The distal lesion appeared after therapy.

on August 31, 1946. He had been referred by a physician because of a skin rash on the legs and arms.

The child had been without complaints until the middle of July, 1945. At that time, he was at home in Savannah, Georgia, where he frequently played in the yard without shoes or stockings. One evening when he came home his mother noticed raised red "bumps" on his forearms and legs. These apparently did not itch. In 24 hours the lesions began to progress and became extremely pruritic. The family physician made a diagnosis of "creeping eruption." Ethyl chloride was applied locally for about 1 minute to each lesion. This therapy was repeated almost every 4 days until October 1, when there were no more active burrows. The patient remained well until July, when, after he had

of lack of familiarity with this form of skin disease the child was referred to the Harvard Department of Tropical Medicine.

Physical examination revealed about thirty irregularly serpiginous lesions on the arms and legs that showed some evidence of excoriation. The child was not febrile, and there was no other evidence of disease. A stool specimen obtained at that time revealed no intestinal parasites. Ethyl chloride therapy was again instituted, with almost immediate relief and eradication of most of the lesions.

Creeping eruption caused by nonhuman hookworm larvae usually involves one or two species of cat and dog hookworms — *A. braziliense* and *A.*

patients. Real, although limited, insight can be gained, elementary interpretations accepted and synthesized, anxiety reduced, and a program of living that involves a minimum of interpersonal conflicts adopted within the time limitations of the therapy provided in the clinic. Although the patient may not be completely well, he can be taught to recognize the sources of his difficulties and given technics for avoiding most of the larger collisions. Our aim, then, may be summarized by an analogy from the field of physical medicine: when we cannot cure the disease, we try to provide an adequate form of compensation. It is our hope that our compensated neurotic patients may, like compensated cardiac patients, lead successful and satisfying lives, although more restricted than those of normal persons.

SUMMARY

A description is presented of the location, staff, admission policy, clinic procedures, staff training program, therapeutic goals, types of treatment given and results of the Veterans Administration Mental Hygiene Clinic in Boston at the close of its first three months of operation.

Individual psychotherapy is the method of choice, but group therapy plays an important role in the treatment program. The type of group therapy utilized is briefly described.

Analysis of the progress of 228 patients shows that approximately 15 per cent were discharged, that the treatment in 28 per cent had lapsed and that 55 per cent were undergoing active treatment.

CREEPING ERUPTION IN NEW ENGLAND*

A Report of Two Cases

CHARLES U. LOWE, M.D.,† AND DONALD L. AUGUSTINE, Sc.D.‡

BOSTON

ONE of the cases of creeping eruption reported below was attributed to the dog hookworm, *Ancylostoma caninum*, and was actually acquired in Boston. Although frequent enough in tropical and subtropical countries, this infection has been reported only once before in New England, in a patient who became ill in Florida.¹ The clinic to which the patient in Case 1 reported would probably have been confounded by his skin lesion had he not brought with him a note from a physician in Louisiana who had made the proper diagnosis. The patient in Case 2 had previously suffered from creeping eruption, and the appearance of the lesion was known to his mother, so that the problem of initial diagnosis was not present. Since this peculiar lesion may occur oftener in New England, this report should aid in its immediate recognition.

CASE 1 (C. H. 308407) R. V., a 2½-year-old boy, was first seen on August 13, 1946, in the Medical Out-Patient Department of the Children's Hospital, because of a localized skin lesion. Accompanying him was a note from the Station Hospital at Camp Pope, Louisiana, stating that the patient had been treated on August 1 with ethyl chloride because of "hookworm infection of the left foot." The social and past histories were noncontributory.

The patient had been well until July 28, when he was living with his mother and father, a lieutenant in the Army, at Camp Pope. He had been permitted to play outdoors unrestrictedly and had frequently been observed playing

without his shoes. On July 28 the mother first noted a large red papule on the left foot between the first and second toes. This was evidently pruritic and kept the patient awake at night. Two days later the lesion had become about 12 cm. long and described a circinate course over the dorsum of the foot. On August 1 the patient was seen at the camp hospital, and a diagnosis of "hookworm disease of the skin" was made. Local ethyl chloride therapy was instituted. Subsequently, a moderately severe slough resulted. Penicillin ointment was applied over the lesion, which healed without complications. On August 3 the family departed for Boston, where they took up residence with the maternal grandparents. Four days later the mother noted two new papules, one over the left tibia and one on the flexor surface of the right forearm. On August 12 the papules had changed to circinate lesions 2 to 3 cm. long. Pruritus again became troublesome, and the child was unable to sleep at night. Because of this, medical advice was sought.

Physical examination revealed an apparently well developed and well nourished child who was in no distress except for the itching skin lesions. On the left instep an area of new epidermis, 8 by 12 cm. in diameter, was visible. This was healing well. On the flexor surface of the left forearm and over the left tibia were single 4-cm. long, irregular, raised, serpentine lesions 2 mm. wide and surrounded by evidence of recent excoriation. Occasional vesicles, 2 mm. in diameter, were present on either side of the burrows. The rest of the physical examination was of no consequence. Since a consultation with the Department of Tropical Medicine, Harvard Medical School, could not be obtained until August 17 the mother was instructed to treat the lesions with calamine lotion in an attempt to control the itching, and to return for consultation.

On August 17 a new eruption had appeared on the left biceps within the previous 24 hours. This lesion was similar to those previously noted. Consultation confirmed the diagnosis of creeping eruption, and therapy with carbon dioxide snow was advised. Three days later examination of the blood disclosed a red-cell count of 3,800,000, with a hemoglobin of 74 per cent (10.5 gm.) and a white-cell count of 10,300, with 39 per cent neutrophils, 50 per cent lymphocytes, 3 per cent monocytes and 8 per cent eosinophils. Examination of the patient's stools on two occasions was negative for intestinal parasites.

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On August 23, the carbon dioxide snow was administered. A week later the child returned because of failure of the lesions on the right forearm and left leg to respond. The lesion on the right forearm was 4 cm long, red, raised and circinate (Fig. 1). Freezing therapy was again instituted. When the patient was seen last on September 13, the eruption on the left leg was still present.

CASE 2 R. C., a 5½-year-old boy, was first seen at the Department of Tropical Medicine, Harvard Medical School,

played in a pit in which cats were known to have defecated about thirty new, red, raised bumps were noted on the arms and legs. These lesions apparently appeared within 4 hours after the child became infected. As before, the macules were nonpruritic until the elongation of the burrows was apparent. Thereafter, the child was annoyed by itching. About August 1 the family left Georgia for a visit to the grandparents in New Hampshire. Owing to the severe itching, a physician was called to see the child. Two weeks later a differential count revealed an eosinophil count of 40 per cent. Because



FIGURE 1 Case 1

This photograph of the right forearm was taken on August 30. A central area of granulation tissue is present in the area that had received carbon dioxide-snow therapy one week previously. The burrow proximal to this had almost healed. The distal lesion appeared after therapy.

on August 31, 1946. He had been referred by a physician because of a skin rash on the legs and arms.

The child had been without complaints until the middle of July, 1945. At that time, he was at home in Savannah, Georgia, where he frequently played in the yard without shoes or stockings. One evening when he came home his mother noticed raised red "bumps" on his forearms and legs. These apparently did not itch. In 24 hours the lesions began to progress and became extremely pruritic. The family physician made a diagnosis of "creeping eruption." Ethyl chloride was applied locally for about 1 minute to each lesion. This therapy was repeated almost every 4 days until October 1, when there were no more active burrows. The patient remained well until July, when, after he had

of lack of familiarity with this form of skin disease the child was referred to the Harvard Department of Tropical Medicine.

Physical examination revealed about thirty irregularly serpiginous lesions on the arms and legs that showed some evidence of excoriation. The child was not febrile, and there was no other evidence of disease. A stool specimen obtained at that time revealed no intestinal parasites. Ethyl chloride therapy was again instituted, with almost immediate relief and eradication of most of the lesions.

Creeping eruption caused by nonhuman hookworm larvae usually involves one or two species of cat and dog hookworms — *A. braziliense* and *A.*

patients. Real, although limited, insight can be gained, elementary interpretations accepted and synthesized, anxiety reduced, and a program of living that involves a minimum of interpersonal conflicts adopted within the time limitations of the therapy provided in the clinic. Although the patient may not be completely well, he can be taught to recognize the sources of his difficulties and given technics for avoiding most of the larger collisions. Our aim, then, may be summarized by an analogy from the field of physical medicine: when we cannot cure the disease, we try to provide an adequate form of compensation. It is our hope that our compensated neurotic patients may, like compensated cardiac patients, lead successful and satisfying lives, although more restricted than those of normal persons.

SUMMARY

A description is presented of the location, staff, admission policy, clinic procedures, staff training program, therapeutic goals, types of treatment given and results of the Veterans Administration Mental Hygiene Clinic in Boston at the close of its first three months of operation.

Individual psychotherapy is the method of choice, but group therapy plays an important role in the treatment program. The type of group therapy utilized is briefly described.

Analysis of the progress of 228 patients shows that approximately 15 per cent were discharged, that the treatment in 28 per cent had lapsed and that 55 per cent were undergoing active treatment.

CREeping ERUPTION IN NEW ENGLAND*

A Report of Two Cases

CHARLES U. LOWE, M.D.,† AND DONALD L. AUGUSTINE, Sc.D.‡

BOSTON

ONE of the cases of creeping eruption reported below was attributed to the dog hookworm, *Ancylostoma caninum*, and was actually acquired in Boston. Although frequent enough in tropical and subtropical countries, this infection has been reported only once before in New England, in a patient who became ill in Florida.¹ The clinic to which the patient in Case 1 reported would probably have been confounded by his skin lesion had he not brought with him a note from a physician in Louisiana who had made the proper diagnosis. The patient in Case 2 had previously suffered from creeping eruption, and the appearance of the lesion was known to his mother, so that the problem of initial diagnosis was not present. Since this peculiar lesion may occur oftener in New England, this report should aid in its immediate recognition.

CASE 1 (C. H. 308407). R. V., a 2½-year-old boy, was first seen on August 13, 1946, in the Medical Out-Patient Department of the Children's Hospital, because of a localized skin lesion. Accompanying him was a note from the Station Hospital at Camp Pope, Louisiana, stating that the patient had been treated on August 1 with ethyl chloride because of "hookworm infection of the left foot." The social and past histories were noncontributory.

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man. Two naturally acquired infections with the former are recorded from the Philippine Islands,⁹ and a third infection has been reported in a boy in Texas.⁷ It therefore appears that man is highly resistant to infection with *A. caninum* and that the infective larvae of this species seldom leave the dermal tissues, where they are effectively destroyed. *A. braziliense*, which is more successful as a human intestinal parasite, is a relatively frequent intestinal parasite of man throughout the Orient and is rare in the Amazon Valley, Brazil.¹⁰ Only one such infection has been noted in the United States.⁷ This occurred in the same boy in Texas who was also infected with *A. caninum* and *Necator americanus*. Individual infections have always been light.

The relative frequency of human intestinal infection with *A. braziliense* in the Orient and its apparent absence in the Western Hemisphere have suggested a duality of types — that is, an oriental type, which has become better adapted to the human host, and an occidental type, which is merely in the first stage of adaptation. The fact that creeping eruption, the manifestation of host resistance, is common in the southeastern states where human intestinal infection with this hookworm is virtually unknown, and the absence of creeping eruption and the rather frequent intestinal infections with *A. braziliense* in the Philippine Islands, as reported by Africa,¹¹ support the view that two distinct types of this species exist.

Creeping eruption is relatively rare among Negroes. Dove⁷ reported that of 301 cases of creeping eruption at Jacksonville, Florida, only 5 (1.6 per cent) occurred in Negroes. There is also a marked racial difference in the incidence and intensity of hookworm infection (*N. americanus*). In endemic areas and when living under almost identical conditions of sanitation, economic status, occupation, soil, temperature and rainfall, the Whites characteristically have a heavy hookworm infection whereas the Negroes have a light one.¹² There is no explanation of this fact, but it is believed to be due to a physiologic difference in the two races — namely, the much greater thickness of the epidermis of the Negro, which provides a natural barrier against infective hookworm larvae.

In view of the fact that *A. caninum* is a relatively frequent parasite of dogs in New England, the question arises concerning the reason for the rarity of creeping eruption in the human population. *A. caninum* occurs most frequently in New England kennels. The infection is rare in stray and vagrant dogs, but is a characteristic infection of puppies. Well-nourished adult dogs are highly resistant to hookworms.¹³ Puppyhood is of relatively short duration and the hookworms acquired in a kennel are self-eliminated as the dog matures. Accurate data are not available, but it is highly probable that for most New England farm dogs and house pets harboring hookworms, the infections are light. The lack of a sufficient number of consecutive days

with favorable temperature and moisture for larval growth of the parasite in New England soil, together with light hookworm infections in the dogs, does not permit the development of a heavy soil infection under most circumstances. Only in kennels and under unusual conditions, such as those in Case 2, are soil infections likely to become sufficiently heavy and concentrated to cause creeping eruption. The apparent absence of creeping eruption among kennel owners and workers in New England may be attributed to the wearing of footgear which adequately protects the skin against immediate contact with hookworm larvae in the soil.

Thus far the most satisfactory treatment for creeping eruption is local freezing applied to the skin in the advancing area of the lesion. Either carbon dioxide snow or ethyl chloride spraying may be used.¹⁴ Fuadin (antimony biscatechol disulfonate of sodium) has been tried with variable success.^{15,16} A yearly fecal examination of pet dogs and cats, with anthelmintic treatment to those found positive for hookworms, would provide a practical precautionary measure.

SUMMARY

Two cases of creeping eruption are reported, one of which was certainly caused by *Ancylostoma caninum* of canine origin and was acquired in Boston. The second case, acquired in Georgia and observed in Boston, was probably caused by *Ancylostoma braziliense*. A review of the literature failed to reveal any other case of creeping eruption due to a hookworm larvae acquired in Massachusetts.

Factors probably responsible for the rarity of creeping eruption in New England are considered.

REFERENCES

1. Gurd, J. L. Creeping eruption (larva migrans): report of case. *New Eng. J. Med.* 201:579-582, 1929.
2. Saries, M. P. Quantitative studies on dog and cat hookworm, *Ancylostoma braziliense*, with special emphasis on age resistance. *Am. J. Hyg.* 10:455-475, 1929.
3. Loos, A. *The Anatomy and Life History of Ancylostoma duodenale* (Dakin). 615 pp. Cairo: Ministry of Public Instruction of Egyptian Government, 1911.
4. Augustine, D. L. Soil infestation with hookworm in southern Alabama from October, 1923 to September, 1924. *Am. J. Hyg.* (Suppl.) 6:67-79, 1926.
5. Augustine, D. L. and Smillie, W. G. Relation of type of soils in Alabama to distribution of hookworm disease. *Am. J. Hyg.* (Suppl.) 6:56-62, 1926.
6. Augustine, D. L. Investigations on control of hookworm disease: further observations on migrations and position of infective hookworm larvae in soils. *Am. J. Hyg.* 3:416-419, 1923.
7. Dove, W. E. Further studies on *Ancylostoma braziliense* and etiology of creeping eruption. *Am. J. Hyg.* 15:664-711, 1932.
8. Hunter, G. W. III and Worth, C. B. Variations in response to filariform larvae of *Ancylostoma caninum* in skin of man. *J. Parasitol.* 31:366-372, 1945.
9. Manalang, C. Studies on ankylostomians in Philippines. *Tr. Sixth Biennial Congress Far Eastern Assoc. Trop. Med.* Tokyo. Pp. 351-368, 1925.
10. Darling, S. T. *Ancylostoma braziliense* de Faria, 1910, and its occurrence in man and animals. *Am. J. Hyg.* 4:416-448, 1924.
11. Africa, C. M. Studies on experimental creeping eruption in Philippines. *Philippine J. Sc.* 48:89-101, 1932.
12. Smillie, W. G. and Augustine, D. L. Intensity of hookworm infection in Alabama: its relationship to residence, occupation, age, sex and race. *J. A. M. A.* 85:1958-1963, 1925.
13. Foster, A. O. and Cort, W. W. Relation of diet to susceptibility of dogs to *Ancylostoma caninum*. *Am. J. Hyg.* 16:241-265, 1932.
14. Mackie, T. T., Hunter, G. W. III and Worth, C. B. *A Manual of Tropical Medicine*. 727 pp. Philadelphia and London: W. B. Saunders Company, 1945.
15. Wilson, J. F. Treatment of creeping eruption with fuadin. *J. Florida M. A.* 30:425, 1944.
16. Rubin, S. S. Creeping eruption. *J. A. M. A.* 124:663, 1944.

caninum Whereas both species are frequent intestinal parasites of both hosts, *A. braziliense* occurs oftener in cats and *A. caninum* occurs more frequently in dogs. Both are world wide in distribution, *A. braziliense*, which is widely established in tropical and subtropical countries, is not normally found in North America as far north as Baltimore.² Although *A. caninum* is likewise widely distributed throughout the warm countries, it differs from *A. braziliense* in that its range extends well into temperate climates. It is a frequent and important parasite of dogs in New England.

The first accurate knowledge of the life history of hookworms was gained from the experimental studies with *A. caninum* by Looss³ in 1911. Eggs, which are the product of the adult male and female worms in the intestine, are deposited on the soil with the feces of the infected host. Development of the embryo is rapid, and hatching occurs in about twenty-four hours. The young hookworm larva, which feeds on bacteria in its environment, reaches its third stage of development — the infective stage — within about five days. Favorable temperature, moisture and type of soil are primary requisites for this development.^{4,5} Having reached the infective stage, the larva no longer feeds during its free existence, its main function is to carry the species to a new host. In moist soil it remains extended from the uppermost soil particles, singly or in large aggregates, within the immediate area of soil pollution.⁶ When these infective larvae, which are markedly thermotropic, are transferred to the skin of warm-blooded animals, activity is greatly aroused, and almost immediately the larvae begin boring into the tissues. Once within the proper host, the infective larvae quickly leave the dermal tissues, enter the lymphatic vessels, and after a circuitous migration, arrive in the small intestine, where they become adult male and female worms.

When infective hookworm larvae invade the skin of a foreign or refractory host, they frequently fail to leave the dermal tissues, through which they burrow indefinitely, producing indurated, sinuous tunnels that progress at the rate of several millimeters to a few centimeters each day. Without intervention, such larvae may continue their migration for weeks or months. This behavior is characteristic of cat and dog hookworm larvae attempting to infect the human body.

A stinging, prickling sensation may be experienced at the time the larvae invade the skin. The first visible lesions — maculas and papules — usually appear after the second or third day of infection, tunnel formation beginning on or after the fourth day of infection. As the advancing end of the line progresses, the opposite end fades away.

Differences have been noted in experimental infections in the type of lesion caused by *A. braziliense* and *A. caninum*.⁷ The lesions caused by the former are characteristically continuous with the points

of entry of the larvae, whereas those of the latter may be discontinuous, apparently because these larvae penetrate the deeper tissues and later return to the surface of the skin at some distance from the point of entry. Marked variations have also been noted in different persons following experimental or accidental infection with a known species.⁸ Therefore, it is not possible to make a specific diagnosis on the character of the lesion or to identify the species on larvae excised from a lesion. The most helpful definitive differential diagnostic method is the isolation of adult hookworms from the small intestine of the animal presumably responsible for the human infection. The diagnosis of *A. caninum* infection was made in Case 1 by means of this procedure.

The fact that new lesions in Case 1 appeared two weeks after the patient arrived in Boston clearly suggested that these last lesions had been acquired locally and that the source of infection was nearby. On questioning, it was learned that the family pet was a five-and-a-half-month-old cocker spaniel that had been acquired in Louisiana and had accompanied the family to Boston. A stool from the dog was examined on August 19 and found to be positive for hookworm eggs. On the request of the mother, the dog was sacrificed at the Angell Memorial Hospital. At autopsy, twenty-two male and thirty-four female *A. caninum* were removed from the small intestine. Since this dog appeared to be the only source of infection, it was concluded that the lesions in this patient were caused by that organism. No specific diagnosis was possible in Case 2. Since, however, cats, but not dogs, were on the premises in Savannah, it is likely that the causative agent was *A. braziliense*.

To complete the study of the patient in Case 1, soil samples were taken from around the house of the family to determine areas of soil infection. This house, typical of many in eastern cities, had a small enclosed back yard, which limited the excursions of both the boy and the dog. Most of the enclosure was so overgrown with bushes and tall grass that the boy's play yard was largely restricted to a small area under a rear porch and its steps, which was also the habitual place in which the dog defecated. Almost continuous rains since the arrival of the family in Boston rendered this particular spot ideal for the development of hookworm larvae.^{4,6} On completion of selection of soil samples, it was learned that the mother had flooded the area with boiling water the day the dog had been sacrificed. No hookworm larvae were found in any of the soil samples. Since no new lesions have been acquired, it appears that the use of boiling water had effectively destroyed any hookworm larvae in the area.

Despite the common occurrence of creeping eruption in certain parts of the world, *A. caninum* and *A. braziliense* seldom cause intestinal parasitism in

and upper two lumbar vertebrae without dividing the muscle. Otherwise, the extent of the operation remained unchanged — that is, removal of sympathetic trunks from the eighth thoracic to the first or second lumbar ganglion, inclusive, and of the great splanchnic nerves from the celiac ganglions to the midthoracic level. Poppen⁹ removed a segment of the tenth or eleventh rib, instead of the eleventh and twelfth, and obtained a lumbar exposure below the twelfth rib, working above and below the diaphragm without dividing the latter. The extent of the removal of the sympathetic trunks and splanchnic nerves is from the seventh or eighth thoracic segment to the second or third lumbar ganglion. More recently, Hinton and Lord¹⁰ suggested a variation in which a segment of the ninth or tenth rib is removed, the diaphragm is divided transversely from above and the sympathetic trunks, together with the splanchnic nerves, are removed as a rule from the third or fourth thoracic segment to the second lumbar ganglion inclusive. The operation is carried out either extrapleurally or transpleurally. They correctly point out that this operation is of greater magnitude and more serious for the patient, and that it is entirely conjectural whether the late results will show any greater benefit. If my concept of the origin of the vasoconstrictor nerves to the splanchnic bed is correct, it does not seem likely that these more extensive procedures will result in a more thorough denervation of this area. From my point of view, the most logical reason for extending this operation is to include the cardiac innervation, which the variations mentioned above do not accomplish. In a number of failures following lumbodorsal splanchnicectomy I have extended the operation subsequently to total sympathectomy to include the heart, so far without notable success. It is possible, however, that in certain cases cardiac denervation should be a part of the original maneuver. It is believed that lumbodorsal splanchnicectomy as described^{5, 11, 12} is the procedure of choice in the great majority of selected cases of continued hypertension because it offers a 75 to 85 per cent chance for improvement at an operative risk of less than 1 per cent.¹²

Results of Surgical Treatment

Peet¹⁴ has recently discussed the late results in a series of 437 cases operated on by his supradiaphragmatic technic. The patients had been followed for five to eleven years. In 82 per cent serious organic disease was demonstrable prior to operation. Two hundred and fifty-one, or 57.5 per cent, were alive at the time of follow-up study.

Of patients with symptoms and fundus changes but without cerebral, cardiac or renal involvement, 95 per cent were living five to eleven years after operation. These represented 17 per cent of the total series. Of these, 30 per cent had normal blood

pressures, and another 47 per cent had maintained significant reductions. Symptoms had been completely relieved or definitely improved. Angiospastic retinal changes had been improved in a remarkably high percentage of cases. Normal electrocardiograms, heart size and kidney function had been adequately protected. Approximately a third of all the patients who showed preoperative evidence of organic heart disease, cerebrovascular disease or impaired kidney function did not survive five to eleven years. Half the patients who fell into these categories maintained significant blood-pressure reductions for the same period of observation. Symptomatic improvement occurred in a high percentage, apparently being present in as many of this group as in the most favorable cases mentioned above. Sixty per cent of patients who had suffered a cerebral accident had no recurrence of this complication after splanchnicectomy.

Of the cases with malignant hypertension, 19 per cent were alive five to eleven years after operation. These patients had severe neuroretinitis with papilledema of 1 diopter or more prior to operation. The usual mortality for such cases prior to the advent of surgery was approximately 80 per cent within one year, 90 per cent within two years and 99 per cent within five years.¹⁵

Experiences with lumbodorsal splanchnicectomy in the treatment of hypertension and hypertensive cardiovascular disease have been discussed by Ayman and Goldshine,¹⁶ de Takats, Heyer and Keeton,^{17, 18} Hinton and Lord,¹⁹ Ray,²⁰ and Smithwick^{11-13, 21, 22} and in numerous communications by White et al.²³⁻³⁰ These authors appear to be in agreement that surgery is a useful adjunct in the management of the hypertensive patient. White et al. have emphasized the favorable changes observed in the hypertensive heart, particularly improvement as demonstrated in the electrocardiograms and heart size and function. Favorable changes also occur in eyegrounds and in renal function as judged by ordinary tests, as well as symptomatic improvement. The early indications are that life expectancy will be materially improved.

Selection of Patients for Surgery

In a recent review of the results of lumbodorsal splanchnicectomy in a series of 439 cases followed for one to eight years, the selection of patients for surgical treatment is discussed in considerable detail.¹² A standard method of study is described that was designed to obtain similar data in all cases and thus to subdivide patients into more comparable categories. All the cases in this series had reached the stage of continued hypertension, and 97 per cent had demonstrable cardiovascular damage prior to operation. These were an unselected group of patients. Over 60 per cent were improved when judged by both blood-pressure data and favorable changes in cardiovascular damage. These results

MEDICAL PROGRESS

SURGERY OF THE AUTONOMIC NERVOUS SYSTEM

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THE following phases of the surgery of the autonomic nervous system will be considered: operations on the sympathetic division, the pathologic and physiologic aspects of the hypertensive state, and operations on the parasympathetic division.

OPERATIONS ON THE SYMPATHETIC DIVISION

The treatment of hypertension and hypertensive cardiovascular disease by operations on the sympathetic division of the autonomic nervous system continues to be the topic of greatest current interest in this field of surgery. The rationale was well stated by Rowntree and Adson¹ in 1925 in what appears to be one of the first articles on this subject. The authors discussed their experiences with 2 patients treated, respectively, by periarterial sympathectomy of the left femoral artery and lumbar sympathectomy. Since the treatment of a great many patients with malignant hypertension had ultimately been disappointing, it occurred to Rowntree and Adson that relative freedom from vascular spasm might be attained through the removal of the vasoconstrictor influence of the sympathetic nerves on the vessels of the leg. It was thought that this might not only lower the systemic blood pressure but also provide simultaneously an area of diminished resistance that would give way under strain and thereby serve somewhat in the capacity of a safety valve for the protection of the cerebral and retinal vessels. In other words, it was their concept that sympathectomy might decrease the peripheral resistance to blood flow and thus result in a lowering of the blood-pressure levels. Also, fluctuations of blood pressure might be minimized, the intermittent stress and strain on the vascular bed being thereby reduced. Although over twenty years have passed since this original attempt to modify the course of hypertensive cardiovascular disease by therapy of this sort and although various suggestions have been made to account for favorable results, no likelier explanation has been advanced to date. Proof of the nature of the effect must await detailed physiologic studies before and after operation. These, unfortunately, have not as yet been carried out in sufficient detail to be conclusive. Discussion so far has therefore centered about objective evidence, such as changes in blood pressure

or the reversal of cardiovascular damage that existed prior to operation.

Extent of Operation

Because periarterial sympathectomy and lumbar sympathectomy had little effect on blood pressure, Adson,² in 1930, extended the operation to include the splanchnic bed. A laminectomy was performed, and the anterior roots were sectioned bilaterally from the sixth thoracic to the second lumbar segment, inclusive. This operation was much more effective but had to be abandoned because of the high mortality and morbidity. Alternate procedures were developed in fairly rapid succession, including the subdiaphragmatic technic of Craig³ in 1934, the supradiaphragmatic splanchnicectomy of Peet⁴ in 1935 and the lumbodorsal or thoracolumbar splanchnicectomy of Smithwick⁵ in 1940. These operations have a similar purpose—namely, to denervate a large vascular area (the splanchnic bed) that contains a large portion of the arterioles of the body. It is generally believed that in hypertensive patients, the increased peripheral resistance to blood flow is offered by vessels of this size. The operative mortality has been low. In 1941 Grimson⁶ suggested that total thoracic or total sympathectomy might be more effective. The purpose of these more extensive procedures was to include the heart in the denervated area. Grimson was led to believe that this was indicated as a result of his experiences with dogs in which experimental neurogenic hypertension could not be significantly modified unless the heart was included in the denervated area. As might have been expected, the mortality of these more extensive procedures was considerably higher than that of the various forms of splanchnic denervation mentioned above. The percentage of successes in unselected cases seemed not appreciably higher than that for the lumbodorsal technic, although it should be stated that Grimson's series was not large enough to be fairly evaluated at that time. Further reports will be awaited with interest. In a recent review Grimson⁷ expressed the opinion that clinical experience with the treatment of hypertension indicated that elimination of abnormal reflex vasoconstrictor tone of central origin more effectively reduces blood pressure as sympathectomy of the body is made more and more complete.

In the recent literature a number of articles have appeared describing modifications of the lumbodorsal technic. Klemme and Woolsey⁸ separated the diaphragm from the bodies of the twelfth dorsal

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to this school of thought. Physiologic studies particularly renal-clearance observations by Smith⁴¹ abundantly corroborated by others,⁴² have together with biopsy material,^{43, 44} cast considerable doubt on the primacy of renal arteriolar disease as the usual causative mechanism. The evidence has been reviewed in some detail, the essential conclusions being that data pertaining to the gross appearance of the kidneys, accumulated during the course of the surgical treatment of hypertensive patients indicate clearly that contracted granular kidneys do not antedate the hypertensive state in man. The following conclusions are drawn^{45, 46}

For the first time, an opportunity for the microscopic study of renal arterioles of living patients with continued hypertension has presented itself. The findings are also at variance with autopsy material. They suggest that pre-existing renal arteriolar disease of a moderate or marked degree is not a *sine qua non* to the hypertensive state.

For the first time, an opportunity has arisen whereby the pathological changes can be correlated with the physiological state of the kidney. It has been noted that neither a marked reduction in quantity (ischemia) nor a change in the nature of renal blood flow (constriction of the efferent glomerular arterioles) is obligatory to the hypertensive state.

When renal vascular disease and hypertension are associated, it is difficult to disprove a cause and effect relation, and no one questions the importance of renal disease when present, as a factor in human hypertension. However, to make this the universal explanation for hypertension in man is not in keeping with the facts. A concept is needed, which will explain the cause of hypertension in the absence of kidney disease, and the absence of hypertension in the presence of kidney disease.

The surgical treatment of hypertension has introduced a new factor, the autonomic nervous system, into the already complicated picture of the hypertensive state in man. It has contributed data which cast doubt upon the primacy of renal arteriolar disease as the sole causative factor.

It is most desirable that the explanation for reduction of blood pressure following splanchnicectomy be determined, since this may lead to a clearer understanding of causative mechanism. It might also lead to the development of accurate methods of selecting cases for this form of treatment. It might indicate productive lines for future investigative work. More detailed studies of the cardiovascular system in hypertensive patients are obviously indicated and may yield information of great value that cannot necessarily be obtained in the experimental laboratory. Collaborative efforts of physiologists, pharmacologists, biochemists and clinicians are needed to accomplish this purpose. Already, a beginning has been made in this direction, and important evidence is being accumulated as a result of such studies. Talbott et al⁴⁴ measured the blood flow through the renal area before and after lumbodorsal splanchnicectomy in a series of 20 cases. Prior to operation a wide variation was noted — from normal levels to a marked reduction. The authors were unable to detect any significant alteration in renal blood flow after operation regardless of the effect on the blood pressure. Further studies of this sort are indicated. More recently, Stewart et al⁴⁷ studied the part of the volume out-

put of blood from the heart that is allotted to the peripheral circulation. These observations were made in normal subjects and in patients with hypertension. A trend toward a decrease in peripheral blood flow was found when there was hypertension, with a rise in the rectal and a decrease in the average weighted skin temperature. The temperature of the upper part of the body was warmer and that of the lower part cooler in hypertensive subjects than in those in the same age groups with normal blood pressures. The reduction in peripheral blood flow to the lower part of the body is greater than the increase in the upper part of the body so that the net result is an average peripheral blood flow for the whole body in hypertensive subjects that is less than the value in normal young men at the same room temperature.

Stewart et al⁴⁸ studied the peripheral blood flow in a series of hypertensive patients before and after splanchnicectomy by various techniques. They found lumbodorsal splanchnicectomy to have the greatest effect on the blood pressure. Following this operation, the blood flow in the upper portion of the body, which tended to be increased in hypertensive patients prior to operation, consistently fell somewhat. In the trunk and lower portion of the body where the tendency in untreated hypertensive patients was toward a decrease, the blood flow remained the same or increased. An increase in blood flow was consistently noted in the distal portion of the lower extremity. The over-all amount of blood allotted to the periphery in hypertensive patients in whom the blood pressure fell to normal after operation increased in some patients and decreased in others. The change was not statistically significant. In another group of patients in whom there was no lowering of blood pressure following operation, the change in peripheral blood flow was not significantly different from that in the group mentioned above. These findings are similar to those of Talbott et al⁴⁴ and others^{49, 50} regarding blood flow through the renal area before and after splanchnicectomy, there being no obvious relation between blood flow and blood pressure. Stewart et al⁴⁸ reached a similar conclusion concerning peripheral blood flow. "The level of blood pressure has no relation to peripheral blood flow either where the blood pressure is high or in the same patient after restoration of normal blood pressure." This viewpoint is of interest and of importance since it is not in keeping with the concept that hypertension is essential to the maintenance of adequate circulation to the tissues that is held by those who believe that elevated blood pressure results from vascular disease and is a compensatory mechanism. It is in keeping with clinical experience indicating that lowering of blood pressure by splanchnicectomy is helpful, not harmful, in the majority of hypertensive patients and is attended by improvement in the state of the cardiovascular system as judged by

were carefully studied, and certain rules were discussed by means of which the patients who had done poorly and those who had the smallest statistical chance for a worth-while result could be excluded with reasonable certainty. The suggested rules apply to about 30 per cent of patients with continued hypertension and cardiovascular changes, leaving 70 per cent that could be regarded as selected cases. In these, there was a 75 to 85 per cent chance for a favorable effect on both the blood pressure and the cardiovascular system following operation. In addition, 113 per cent showed no progression. The total mortality from all causes, including operative mortality and deaths unrelated to the disorder in question, for the follow-up period of one to eight years was remarkably low, 98.8 per cent of the patients being alive at the time the analysis was made. This series comprised many cases with previous cerebrovascular accidents, abnormal electrocardiograms and enlarged hearts and some with congestive failure or previous coronary thromboses, as well as definite evidence of renal disease as judged both by tests of function and by the study of biopsy material obtained at operation. It is expected that a larger experience and a longer follow-up period will suggest further rules designed to improve accuracy in the selection of cases for this form of treatment. Because of the amount of data that have been obtained in the study of each case, it is expected that when the series is larger it will be possible to divide the cases into many smaller groups, so that almost any hypertensive patient will fall into one of them. The effect of surgery of this sort on blood pressure, the cardiovascular system and life expectancy can then be foretold accurately. Such variables as sex, age and the severity of the hypertension — as judged by the resting horizontal diastolic level, the width of the pulse pressure and the state of the brain, eyegrounds, heart and kidneys, as well as the response to sedation and other transient methods of inactivating sympathetic activity — will have to be held constant in each subgroup. One of the great difficulties about any discussion of the results of surgical treatment of hypertensive patients at present is the fact that no such comparable data for nonsurgically treated patients are available for comparison. Consequently, these results are open to as much criticism as anyone wishes to level at them. In any event nobody questions the facts that the complications of hypertension are responsible for more deaths annually than any other human disorder and that a reduction of this mortality rate and an increase in the life expectancy of this group of patients are highly desirable. To meet the objection mentioned above the natural course of a control series of similarly studied patients who have not as yet been subjected to surgery is being followed. It is essential that the method of study be comparable in every respect. It would not be proper,

for example, to compare patients with transient or intermittent hypertension with those who have passed through this phase and have reached the stage of continued hypertension in which the diastolic pressure no longer falls to normal after a period of bed rest. Nor would it be proper to compare cases of continued hypertension without cardiovascular changes with those having damaged vascular beds. The latter is the group with which I have been primarily concerned to date. If a simple panacea for this disorder is ever discovered, it will undoubtedly be found to be most effective if employed before the vascular bed is damaged. The same thing will probably be true of surgical treatment. Earlier operation has been suggested by White,²⁹ Landis³¹ and de Takats.¹⁸

In the recent literature the use of spinal anesthesia by one technic or another has been advocated as a means of selecting cases for surgical treatment.^{22, 23} The data so far presented do not appear to be significant. Also, the effect of newer sympatholytic drugs has been described.^{34, 35} It seems unlikely that any diagnostic procedure that has a transient effect will be the entire answer to this difficult problem. There may be an adequate correlation in patients who respond well to those temporary measures and the effect of operation. There will probably be an unsatisfactory correlation in those who do not respond well to tests but who do benefit by surgery. The matter appears to me to be a little too complex to be amenable to solution in this fashion. It also seems likely that at least a part of the favorable effect of sympathectomy cannot be measured by changes in blood-pressure levels alone.

PATHOLOGICAL AND PHYSIOLOGIC ASPECTS OF THE HYPERTENSIVE STATE

Although the primary purpose of the surgical treatment of these patients has been to lessen the severity of the hypertension, to reverse cardiovascular changes when possible and to increase life expectancy, it has been realized that this approach to the problem has offered a unique opportunity to obtain factual data concerning the pathologic physiology of the hypertensive state. In particular, it has been possible to visualize the kidneys at operation and to obtain specimens for microscopical study. Ever since Richard Bright^{36, 37} first called attention to the entity of hypertension and the role of the kidney in the production of increased tension within the vascular bed, opinions have varied concerning the importance of the renal vascular area in the genesis of this disorder. The demonstration by Goldblatt³⁸ that reduction of blood flow through this area by clamping of the renal arteries resulted in chronic hypertension in animals has further stimulated interest in this matter. The detailed studies of Moritz and Oldt,³⁹ notwithstanding the discussion of this matter in 1872 by Gull and Sutton,⁴⁰ added further impetus

other stimuli, particularly some of an emotional variety, may cause increased vagal activity and acid secretion. There is no reason to doubt that the secretory response to these stimuli is inhibited by vagectomy. Thus, an over-all effect of this operation is to reduce both continuous and intermittent gastric secretion of neurogenic origin. Its efficacy in the treatment of some duodenal ulcers may depend on the extent to which the first period of gastric secretion, the cephalic phase of the second period, and other neurogenic or psychosomatic mechanisms enter into the problem at hand. It is true, however, that in other ulcer patients there is little evidence of an abnormality of neurogenic secretory mechanisms. Whether there will be any great effect on either the gastric or the intestinal phase of the secretory process awaits further study. These are thought to be largely under the control of chemical substances of a histamine-like nature. After vagectomy, a response to histamine or caffeine still persists, although in some cases a reduction has been noted following histamine, as pointed out by Grimson.⁵⁵ The explanation for the latter is not clear.

In addition to these reported changes in gastric secretion, an alteration of gastric and intestinal motility is noted, particularly in the immediate postoperative period. This is evidenced by a delay in the initial as well as the total emptying time of the stomach. Its tone and reactivity are likewise decreased. These changes become less marked in the course of months and are rarely attended by symptoms of consequence. Whether these motility changes have any beneficial effect on the healing of peptic ulceration is not known.

Grimson⁵⁵ believes that although changes in secretion and acidity are important, the most pronounced and consistent change produced by vagectomy is the decrease in motility of the stomach. On the other hand, Dragstedt⁵⁴ points out that in experimental animals in which gastric juice is allowed to be in contact with the intestinal mucosa when the alkaline duodenal secretion has been shunted distally (as in Mann-Williamson dogs) ulcers regularly develop. In these animals the motility factor has probably not been materially altered. In almost all reported cases the relief of symptoms, particularly pain, has been dramatic, immediate and persistent. Nearly all ulcers have healed promptly. The effect of operation has so far been particularly gratifying in the group of troublesome cases in which gastrojejunal ulcerations have developed following gastric resections. The relief from pain is of interest since it is not associated with evidence that pain pathways have been divided as judged by postoperative balloon-distention observations. Pain is still perceived in response to stimulation of the esophagus, duodenum and jejunum⁵⁵ and when hydrochloric acid is introduced into the stomach.⁵⁵ It therefore appears that relief is more probably due to decreased acidity or motility or to both.

Surgical Technique

An excellent review of experimental work in this field and of the earlier attempts to perform an effective interruption of the vagal innervation of the stomach in man was recently published by Weinstein et al.⁶⁰ Partial division of the vagal fibers to the stomach by vagotomy for the relief of peptic ulcer was performed by Suerlin in 1920, Bircher in 1921 and Schiassi in 1925. In 1937 Barron and Curtis divided the left (anterior) vagus nerve in a case of gastric hypertonia. Winkelstein and Berg⁶¹ combined anterior vagotomy with subtotal gastrectomy for duodenal ulcer in patients with high gastric acidity in 1938. In all these operations, an abdominal approach was used. The denervation was only partial.

To study the relative merits of partial and total parasympathetic denervation of the stomach Weinstein et al.⁶⁰ studied the behavior of three types of gastric pouch in dogs: the Heidenhain pouch, which receives no vagus innervation, the Pavlov pouch, in which only a small percentage of vagal fibers remains intact, and the so-called "vagal" pouch, in which practically all the vagal fibers are unsevered. The secretory responses to the ingestion of food, as measured by the acidity curve, were found to be essentially the same in all varieties of pouches. When, however, a stimulus was applied that operated through the nervous system, good secretory responses were noted in the totally and partially innervated pouches, being equally marked in each. This is an important observation, since it confirms a general law that has been previously learned in surgery of the sympathetic nervous system — namely, that a denervation must be complete to be effective. In only the Heidenhain pouches (totally denervated) was there no secretory response to this stimulus. Weinstein et al. believe the insulin test to be an effective indicator of the completeness of denervation following vagectomy in man. It is performed on a fasting stomach with a tube in place. The contents are aspirated, and 15 units of regular insulin is injected intravenously. Following this, gastric specimens are withdrawn every fifteen minutes for three hours, and blood sugar determinations are made at the beginning of the test and every half hour for one and a half hours. In 6 cases in which various types of vagectomies and vagotomies were performed, evidence of incomplete denervation was found after operation as judged by a significant acid secretory response to insulin. This led the authors to conclude that complete parasympathetic denervation of the stomach was impractical in man. Dragstedt et al.⁵⁴ and Moore and his associates⁵⁵ found the postoperative response to insulin to be abolished. Grimson⁵⁶ reported a variable reduction. My own experiences indicate that vagectomy has so far been uniformly successful in abolishing or greatly reducing postoperative

favorable changes in the cerebral, retinal, cardiac and renal areas, as well as in symptoms. Stewart et al also noted that the rectal temperature, which was elevated in hypertensive patients, fell after operation. Also, in patients who experienced a fall in blood pressure to normal there was a decrease in the mean basal metabolic rate. In patients in whom there was no change in blood pressure there was no change in the basal metabolic rate. Studies of this sort are significant, representing the beginning of what must be determined to explain the mechanism whereby blood pressure is lowered following surgery. The crucial questions are whether sympathectomy lowers blood pressure by affecting active causative mechanisms of a physiologic nature, or whether the effect is due to a change in hemodynamics that counteracts hypertension. Why does splanchnicectomy fail to affect hypertension in certain cases? The correct answer to these questions may have an important bearing on the cause of hypertension in man.

OPERATIONS ON THE PARASYMPATHETIC DIVISION

With the exception of sporadic attempts to relieve bronchial asthma by resection of vagal fibers to the lung, little has been attempted in the way of surgery of the parasympathetic nervous system. In recent years reports of experiences with resection of the vagus nerves to the stomach in the treatment of peptic ulcer have appeared in the literature. The early results seem encouraging and suggest that vagectomy may prove to be a useful adjunct to other measures available for the management of this disorder. A widespread interest has developed, and it is to be expected that the possibilities of this therapeutic measure will be explored in many clinics and that the literature on this subject will increase considerably in the next few years. As with everything that is new, the test of time will have to be applied before a final evaluation of results can be made.

Perhaps it is not quite correct to refer to vagectomy as a new procedure. Physiologists have been familiar with it for many years and have studied its effect on gastric function in great detail. One of the earliest references to its application in man is a report by Pieri⁵¹ in 1932. He performed bilateral subdiaphragmatic resection of the vagus nerves in 14 patients for the relief of gastric disorders, and stated that the operation was well tolerated and did not cause appreciable untoward incidents. The report that stimulated current interest in this matter was that of Dragstedt and Owens⁵² in 1943. Their first 2 patients were operated on in January and February of that year. Since that time additional reports of progress have been made by Dragstedt and his associates^{53, 54} Moore et al⁵⁵ and Grimson⁵⁶ have also reported early results.

Rationale of Vagotomy for Peptic Ulcer

In their writings to date, Dragstedt et al have stressed the use of vagectomy in cases of refractory and complicated ulcer. Most of their subjects have been men with long-standing duodenal ulcers with or without previous surgery. They have also stressed the effect of this operation on the first period of gastric secretion — namely, that of interdigestive or continuous secretion. To obtain data on this matter, they collected gastric juice for twelve-hour periods from 9:00 p.m. to 9:00 a.m. by continuous suction, the stomach having been emptied and washed out prior to the collection period. The average findings for at least three such periods of observation prior to operation in 10 patients with refractory ulcer who had had no previous surgery were as follows: volume, 821 cc, free acid, 47 units, and total acid, 66 units. Following operation, the corresponding values were 335 cc, 15 units and 46 units. In 9 cases of complicated ulcer the findings before and after vagectomy were similar. Some of these patients were obstructed, and a gastroenterostomy was also performed; others had had previous gastric resections or gastroenterostomies. In the discussion of the paper in which these results were reported, Grimson indicated that the twelve-hour night-secretion volumes in his series of 18 cases were reduced from an average of 946 cc before operation to one of 342 cc after operation. The acidity expressed in terms of pH was changed from an average of 1.72 before to 3.55 after vagectomy. These findings are of interest, not only because they indicate at least one clear-cut physiologic effect of the operation but also because they cast additional light on the explanation for the period of continuous gastric secretion. As recently as 1941 Ivy,⁵⁷ in an excellent discussion of the mechanisms of gastric secretion, indicated that the nature of the stimuli that give rise to the continuous secretion of gastric juice is uncertain. He stated that some patients, particularly those with a duodenal ulcer, manifested a hypernormal continuous secretion — that is, the stomachs continued to secrete a copious quantity of acid juice after emptying. He suggested that this might be due to the production of histamine by an irritated mucosa, since atropine in relatively large doses does not abolish abnormal continuous secretion whereas it has a significant effect on normal gastric secretion as shown by Keefer and Bloomfield.⁵⁸

In addition to the effect of vagectomy on the first period of gastric secretion, it seems probable that certain aspects of the second are favorably affected. This period may be divided into three phases: the cephalic, the gastric and the intestinal. The first is known to be under the control of the vagus nerves. Stimuli such as sight, smell, taste and thought of food result in gastric secretory activity mediated by the parasympathetic nervous system. Certain

- 13 Hinton J W., and Lord J W. Jr. Surgical treatment of advanced hypertension. *New York Med J* 113 1945
- 14 Conferences on Therapy. Surgical treatment of hypertension. *New York State J Med* 45 2515-2524 1945
- 15 Smithwick R. H. Some experiences with surgical treatment of hypertension in man. *Tr & Stud. Coll Physicians Philadelphia* 12 99-100 1944
- 16 *Ibid.* Experiences with surgical treatment of hypertensive cardiovascular disease in man. *Clin & Clin Quart* 11 10 117 1945
- 17 White P D. Reversibility of heart disease. *Illness M J* 86 9 14 1944
- 18 Rojas F., Smithwick R. H. and White P D. Nonspecific major operations and lumbodorsal sympathectomy: comparison between their effects on blood pressure. *J A M A* 126 17 17 1944
- 19 Evans E., Mathews M. W., and White P D. Electrocardiogram in hypertension. I Its description. *Am Heart J* 30 140-165 1945
- 20 White P D., Smithwick R. H., Mathews M. W. and Evans E. Electrocardiogram in hypertension. II Effect of radical lumbodorsal sympathectomy (preliminary report). *Am Heart J* 30 16-18 1944
- 21 Carabal E. J., Thomson H. F. W. and White P D. Electrocardiogram in hypertension. III. Electrocardiograms of hypertensive patients followed for long time without splanchnic resection in comparison with those in patients who had had splanchnic resection. *Am Heart J* 30 189 194 1945
- 22 White P D. Hypertensive heart 1927 to 1945. *B. N. Eng M J* 70 20 1945
- 23 *Ibid.* Heart in hypertension since days of Pichard Brigh. *Cleveland M J* 34 129 136 1946
- 24 Bridges W. C., Johnson A. L., Smithwick R. H. and White P D. Electrocardiography in hypertension: study of patients subjected to lumbodorsal splanchnicectomy. *J A M A* 131 1476-1480 1946
- 25 La di E. M. Hypertension problem. *Tr & Stud. Coll Physicians Philadelphia* 12 47 58 1944
- 26 Finkel H. L., Southworth J. L. and Zolman B. L. Continuous caudal anesthesia as test in resection of hypertensive patients for sympathectomy. *J A M A* 125 1225 1945
- 27 *Ibid.* Selection of hypertensive patients for sympathectomy. *J A M A* 130 927 934 1946
- 28 Lyons R. H., Moe G. K., Campbell K. N., Neigh R. B., Hoobler S. W., Berry R. L. and Kennick B. R. Effects of blockade of autonomic ganglia in man: preliminary observation on use of tetraethyl ammonium bromide. *Univ Hosp Bili Am J Surg* 12 1946
- 29 Nickerson M., and Goodman L. S. Pharmacology of series of new sympatholytic agents. *Proc Am Federation Cur Research* 2 103 1945
- 30 Bright R. *Reports of Medical Cases Selected with a View of Illustrating the Symptoms and Cure of Diseases by a Reference to Morbid Anatomy*. Vol 3 271 pp. London Longman, Rees, Orne Brown and Green 1827
- 31 *Ibid.* Cases and observations illustrative of renal disease accompanied with secretion of albuminous urine. *Guy's Hosp Rep* 1 338-400 1836
- 32 Goldblatt H. Studies on experimental hypertension. XII. Experimental production and pathogenesis of hypertension due to renal ischemia. *Am J Clin Path* 10 40-72 1940
- 33 Moritz A. R., and Oldt, M. R. Arteriosclerotic sclerosis in hypertensive and non hypertensive individuals. *Am J Path* 13 679 728 1957
- 34 Gull W. W., and Sutton H. G. On pathology of morbid state commonly called chronic Bright's disease with contracted kidney (Arterio-capillary fibrosis). *Med-Chir Trans* 55 273-326 1872
- 35 Smith H. W. *Studies in the Physiology of the Kidney*. 100 pp. Lawrence University of Kansas University Extension Division 1933
- 36 Goldring W., and Chaus H. *Hypertension and Hypertensive Disease*. 253 pp. New York Commonwealth Fund 1944
- 37 Castelman B. and Smithwick R. H. Relation of vascular disease to hypertensive state based on study of renal biopsies from 100 hypertensive patients. *J A M A* 121 1256-1261 1945
- 38 Talbot J. H., Castleman B., Smithwick R. H., Melville R. S. and Pecora L. J. Renal biopsy studies correlated with renal disease observations in hypertensive patients treated by radical sympathectomy. *J Clin Investigation* 22 387 394 1945
- 39 Smithwick R. H. Hypertension as viewed from its surgical treatment. Part I. *Med Current Cardiovascular Dis* 13 December 1944
- 40 *Ibid.* Hypertension as viewed from its surgical treatment. Part II. *Med Current Cardiovascular Dis* 14 January 1945
- 41 Stewart H. J., Evans W. F. and Haskell H. S. Peripheral blood flow under basal conditions in older male subjects with normal and elevated blood pressures. *Am Heart J* 31 743 351 1946
- 42 Stewart H. J., Evans W. F., Haskell H. S. and Brown, H. Effect of splanchnic resection on peripheral blood flow and renal and skin temperatures in hypertension. *Am Heart J* 31 728-743, 1946
- 43 Fox P. P., Woods W. W., Peet M. M. and Fox N. L. Effective renal blood flow glomerular filtration rate and tubular excretory mass in arterial hypertension. *Circ Res* 69 822 835 1942
- 44 Cochrane A. C., and Page I. H. Renal blood flow and sympathectomy in hypertension. *Arch. Surg* 42 1072 1082 1941
- 45 Pieri G. La resezione sottodiaphragmatica dei vaghi. *Arch. Sci Med* 11 53 59 1942
- 46 Dargstedt, L. R. and Owers F. M., Jr. Supradiaphragmatic section of vagus nerves in treatment of duodenal ulcer. *Proc Soc Exptl Biol & Med* 53 152 154 1945
- 47 Dargstedt L. R. and Schafer P. W. Removal of vagus innervation of stomach in gastroduodenal ulcer. *Surgery* 17 742-749 1945
- 48 Thornton T. F. Jr., Storer, E. H. and Dargstedt L. R. Supradiaphragmatic section of vagus nerves: effect on gastric secretion and motility in patients with peptic ulcer. *J A M A* 130 764-771 1946
- 49 Moore F. D., Chapman W. P., Schulz, M. D. and Jones C. M. Transdiaphragmatic resection of vagus nerves for peptic ulcer. *N. Eng J Med* 234 241 251 1946
- 50 Grimson K. S., Taylor H. M., Trent J. C., Wilson D. A. and Hill H. C. Effect of transsternal vagotomy upon functions of stomach and upon early clinical course of patients with peptic ulcer. *Surg. M J* 39 460-472 1946
- 51 Ivy A. C. Mechanisms of gastric secretion. *Surgery* 10 861 873 1941
- 52 Keefer C. S. and Bloomfield A. L. Effect of atropine on gastric function in man: quantitative study. *Arch Int Med* 33 303-320 1946
- 53 Dargstedt L. R. Section of vagus nerves to stomach in treatment of peptic ulcer. *Surg Gynec & Obst* 83 547 549 1946
- 54 Weinstein V. A., Colp R., Hollander F., and Jermann E. E. Vagotomy in therapy of peptic ulcer. *Surg Gynec & Obst* 79 297-305 1944
- 55 Winkelstein A. and Berg A. A. Vagotomy plus partial gastrectomy for duodenal ulcer. *Am J Digest Dis* 5 497-501 1938
- 56 Smithwick R. H. Problem of producing complete and lasting sympathetic denervation of upper extremity by preganglionic section. *Ann Surg* 112 1035-1100 1940

insulin secretion as well as greatly modifying the volume and acidity during the continuous period of gastric secretion. Also, vagectomy has had a greater effect than preoperative atropine block on this period of gastric secretion. In some cases the response to histamine has been definitely reduced.

Successful bilateral vagectomy may be performed by either a transthoracic or an abdominal approach. In the former, an extensive resection of the seventh or eighth rib on the left side is advocated by Dragstedt and Schafer.⁵³ I have found this to give an excellent exposure of the operative field. The vagus nerves are quite readily exposed above the diaphragm and divided at this level. The various branches that form a network about the esophagus are gathered into two bundles and freed for about 10 cm above the diaphragm. The upper ends are sutured widely apart by Dragstedt, and the pleura closed. It has been my custom to encase the nerves in a silk cylinder as a further precaution against regeneration—a maneuver that has been used elsewhere⁶² in surgery of the autonomic nervous system. Moore et al.⁶³ have reported the use of this step in technic and in addition have divided the diaphragm and followed the branches of the vagi to their terminations in the stomach wall for additional protection against regeneration. So far, no definite evidence of this has been reported in the literature following supradiaphragmatic resection. A recent conversation with Dragstedt reveals that the patients in his earliest cases, who were operated on nearly four years ago, continue to do well.

The abdominal approach is useful when some additional procedure is indicated or when exploration of the lesion is considered advisable. In certain cases, particularly those with a high degree of obstruction combined with hypersecretion of the continuous variety, vagectomy has been combined with gastroenterostomy or gastric resection. If the left lobe of the liver is mobilized by division of its peritoneal attachment to the diaphragm, the esophagus is readily exposed. After its anterior peritoneal covering has been incised, dissection can be carried upward quite readily for about 6 cm above the diaphragm, and this portion of both the anterior and the posterior vagus nerves and their branches resected. In proper hands and under ideal circumstances it is apparent that these operations can be performed with an extremely low mortality and with few complications.

The Selection of Cases for Surgery

The writings of Dragstedt et al. have emphasized the significance of the first period of gastric secretion. They have indicated that hypersecretion has been present in the great majority of their patients. Their data suggest that the patients who exhibit this abnormality may be the ones who are likeliest to do poorly after subtotal gastrectomy. So far as the cephalic phase of gastric secretion is concerned,

it appears that studies of sham feeding have not revealed any conclusive evidence of abnormal responses in ulcer patients. Such reactions as exist should be modified by vagectomy. Moore et al. emphasize the importance of the history in ulcer patients, particularly evidence pertaining to the effect of stress and strain on symptoms. They regard young and middle-aged patients, who are most frequently men, with chronic ulcers that recur under stress and strain and are only transiently relieved by food or alkali as ideal subjects for operation. Previous perforation or hemorrhage is not considered a contraindication. Vagectomy should not be performed in their presence. The question of obstruction and its management by additional procedures such as gastroenterostomy and gastric resection remains for future evaluation. Because of increasing evidence pointing toward the danger of carcinoma in the presence of gastric ulceration, it appears inadvisable in general to treat cases of this sort by vagectomy. The early results of vagectomy are encouraging and warrant further study of its use in patients with duodenal ulcers requiring surgical treatment. It will be some time before the relative merits of and the indications for gastric resection and vagectomy are established.

REFERENCES

- Rowntree, L. C. and Adson, A. W. Bilateral lumbar sympathectomy in treatment of malignant hypertension. report of case. *J. A. M. A.* 85:959-961, 1925.
- Adson, A. W. and Brown, G. E. Malignant hypertension. report of case treated by bilateral section of anterior spinal nerve roots from sixth thoracic to second lumbar, inclusive. *J. A. M. A.* 102:1115-1118, 1934.
- Craig, W. M. Surgical approach to and resection of splanchnic nerves for relief of hypertension and abdominal pain. *West. J. Surg.* 42:146-152, 1934.
- Peet, M. M. Splanchnic section for hypertension. preliminary report. *Univ. Hosp. Bull. Ann Arbor* 1:17, 1935.
- Smithwick, R. H. Technique for splanchnic resection for hypertension. preliminary report. *Surgery* 1:1-8, 1940.
- Grimson, K. S. Total thoracic and partial to total lumbar sympathectomy and celiac ganglionectomy in treatment of hypertension. *Ann. Surg.* 114:753-775, 1941.
- Idem*. Sympathectomy and circulation—anatomic and physiologic considerations and early and late limitations. *Surgery* 19:277-298, 1946.
- Klemme, R. M. and Woolsey, R. D. More extensive operation for hypertension. report of cases. *J. Missouri M. A.* 40:241-245, 1943.
- Poppen, J. L. Technic for supradiaphragmatic and infradiaphragmatic sympathectomy for hypertension. *Lakey Clin. Bull.* 3:151-158, 1943. Correction. *Ibid.* 3:187, 1943.
- Hinton, J. W. and Lord, J. W. Jr. Operative technique of thoracic-lumbar sympathectomy. *Surg. Gynec. & Obs.* 83:643-646, 1946.
- Smithwick, R. H. Surgical treatment of hypertension. effect of radical (lumbodorsal) splanchnicectomy on hypertensive state of 156 patients followed one to five years. *Arch. Surg.* 49:180-193, 1944.
- Idem*. Surgical treatment of hypertension. some circumstances under which lumbodorsal splanchnicectomy appears to be inadvisable in hypertensive patients. *New York State J. Med.* 44:2693-2700, 1944.
- Idem*. Surgical treatment of continued hypertension. some suggestions pertaining to selection of cases for this form of therapy. *J. M. Soc. New Jersey* (in press).
- Peet, M. M. and Isberg, E. M. Surgical treatment of essential hypertension. *J. A. M. A.* 130:467-473, 1946.
- Keith, N. M., Wagener, H. P. and Barker, N. W. Some different types of essential hypertension: their course and prognosis. *Am. J. M. Sc.* 197:332-343, 1939.
- Ayman, D. and Goldshine, A. D. Blood pressure determinations in patients with essential hypertension. evaluation of sympathectomy over three year to five-year period. *New Eng. J. Med.* 229:799-811, 1943.
- deTakats, G., Heyer, H. E. and Keeton, R. W. Surgical approach to hypertension. *J. A. M. A.* 118:501-507, 1942.
- deTakats, G., Graupner, G. W., Fowler, E. F. and Jenak, R. J. Surgical approach to hypertension. second report. *Arch. Surg.* 53:111-163, 1946.

The retrograde pyelogram shows good calyces, pelves and ureters on both sides

DR SHORT There is no definite evidence of pneumonia at the time of admission. We also have nothing to suggest any marked degree of pulmonary edema. The patient had no fever when she entered the hospital, which suggests that the infection, whatever it was, had cleared. The high white-cell count can probably be explained by a renal injury.

The next question and the chief one to answer is, What was the cause of the anuria and uremia that were evidently responsible for this woman's death? I am unable to decide from the evidence at hand that any of the usual forms of nephritis were present, although an acute glomerulonephritis secondary to infection could produce a clinical picture somewhat similar to this. The lack of fever is against a suppurative lesion of the kidney, and such rare conditions as dissecting aneurysm involving the renal arteries and renal infarction, I believe, we need mention only in passing.

I am forced to conclude that the renal shutdown was directly connected with the sulfonamide preparation taken by the patient. This preparation, I have been informed, contains 1.5 gm of sulfadiazine and an equal amount of sulfathiazole per 30 cc, with additional sodium citrate and sodium lactate in an aqueous solution, so that we do not need to worry about a toxic solvent's being involved. In the dosage given this patient received 6 gm of each drug, which does not seem excessive over two days, and we know that the solubility of the drugs was probably enhanced by the mixture of equal parts of each drug and by the additional alkali. For this reason, as well as the lack of severe pain, the absence of crystals in the urine and the negative findings on washing of the kidney pelves, I have decided against obstruction of the kidney pelves or the ureters by sulfonamide concretions as the cause of the anuria. These considerations do not rule out obstruction in the tubules themselves by sulfonamide crystals, but I prefer to believe that the anuria was due chiefly to a direct toxic action on the renal parenchyma. Such a process has been clearly described pathologically without evidence of obstruction by crystals, although it is less frequent as a cause of sulfonamide renal impairment than obstruction.

I might mention still another possibility that the renal damage was due to an acute hemolytic anemia resulting from sulfonamide administration. These cases occur nearly always with sulfanilamide, and we should expect jaundice and a severer degree of anemia to be present. As a matter of fact, if such an anemia had occurred, the pathological findings would have been closely similar to those that I expect to be found in this patient.

Before concluding, I should like to attempt to answer a few more questions. It would be interesting to know whether or not previous administration

of sulfonamides had taken place, so that the severity and the abruptness of the reaction could be explained on the basis of hypersensitivity. We are not helped by the history, and there were no other manifestations of sensitivity, such as fever and dermatitis. It is still possible that focal lesions in the heart and other organs will be found or even vascular changes resembling periarteritis nodosa, as described by Rich.^{1,2} But the short duration of administration of the drugs makes this unlikely unless the patient had previously been sensitized. Whether or not she had pre-existing renal disease that had made her especially susceptible to sulfonamide intoxication, I do not believe that we can find out, although the negative pyelogram helps rule out certain anomalies and diseases of the kidney. The site of damage in the group to which I think this patient belonged is usually the distal portion of the tubules, with involvement also of the interstitial tissue—so-called "lower-nephron nephrosis." A similar clinical picture can be produced by cortical necrosis. I have seen a reference to this condition that was presumably caused by sulfonamide intoxication,³ but I do not believe that we need consider it in the case under discussion.

In summary, I believe that the primary cause of death in this patient was uremia resulting from tubular necrosis caused by sulfonamides, with cardiac enlargement and arteriosclerosis as additional diagnoses. I do not believe that I can say anything about the changes in the lungs, unless edema developed before death. In a woman of this age other abnormalities or landmarks may well have been present, but I shall not try to predict what they were.

DR TRACY B. MALLORY Dr Dahl, will you tell us what the impression was on the ward?

DR LOUIS K. DAHL In general the house staff believed that the diagnosis rested between three main possibilities: acute glomerulonephritis, with sudden shutdown, interstitial nephritis due to sulfonamides, and—one person thought—bilateral cortical necrosis. The most prevalent opinion was interstitial nephritis caused by sulfonamides.

CLINICAL DIAGNOSIS

Interstitial nephritis, caused by sulfonamides

DR SHORT'S DIAGNOSES

Lower-nephron nephrosis, due to sulfonamide toxicity

Cardiac enlargement

Arteriosclerosis

ANATOMICAL DIAGNOSES

Periarteritis nodosa

Diffuse cortical necrosis, secondary

Arteriosclerosis

Hypertrophy of heart

Pulmonary emphysema

Cholelithiasis

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CASE 33181

PRESENTATION OF CASE

An eighty-nine-year-old widow entered the hospital from a convalescent home because of oliguria.

The patient was unable to give a reliable history, and the only information that bore up under repeated questioning was that three weeks before hospital entry she had developed a cough productive of thick, yellow sputum and fever, nausea and abdominal soreness, with anorexia so severe that she took little food or water. Her physician disclosed that she had been given 120 cc of Aldiazol, a liquid sulfadiazine preparation, over a two-day period. Four days before entry the urinary output dropped markedly, so that only 180 cc of urine had been passed in the forty-eight hours before admission. The patient had previously noted darkening and reddening of the urine, but the volume seemed to have remained fairly normal. She denied backache and dysuria. Although she had eaten little during this time, she had drunk considerable fluid.

The past history revealed that she had had shortness of breath on exertion but no anginal pain. For several years she had taken digitalis irregularly. She had long been constipated and had used laxatives regularly for more than a year. She had never had any children, the ovaries having been removed many years previously for an unknown reason.

Physical examination revealed a moderately obese woman with a dry tongue. Although the memory was poor, she was alert and co-operative. The chest was emphysematous, with a moderate number of fine moist rales at both bases posteriorly. The area of cardiac dullness was obscured by emphysema. No murmurs were heard. There was slight tenderness in the right upper quadrant. The liver and spleen were not palpable. There was tenderness in both costovertebral angles, especially on the right. Pelvic examination revealed some tenderness on motion of the cervix upward. No masses were felt.

The temperature, pulse and respirations were normal. The blood pressure was 130 systolic, 65 diastolic.

Three cubic centimeters of dark-brown urine was obtained by catheter, and analysis showed a pH of 7.5, a + test for albumin and no sugar, the sediment contained numerous fresh red cells, many

epithelial cells and 1 or 2 white cells per high-power field. No bacteria or casts were noted. Examination of the blood disclosed a red-cell count of 4,100,000, with a hemoglobin of 10.5 gm, and a white-cell count of 24,000, with 91 per cent neutrophils. The nonprotein nitrogen was 133 mg per 100 cc. The sodium was 137.3, the potassium 6.3, the carbon dioxide 31.0 and the chloride 95 milliequiv per liter. The blood was examined for sulfadiazine, but no trace was found.

X-ray examination of the chest showed cardiac enlargement, the cardiothoracic ratio being 13.23, but the configuration was not characteristic of a particular lesion. The wall of the aorta showed calcification. No fluid was present in the pleural sinuses, and there were irregular areas of increased density at both bases. The pulmonary markings were everywhere a little prominent, but no gross areas of collapse or consolidation were seen. A plain film of the abdomen showed gas-filled loops of large bowel and of a portion of the small bowel, possibly ileum. Cystoscopy and retrograde pyelograms were negative. No urine, however, was obtained from either pelvis. Instilled fluid returned clear from the right pelvis and slightly blood tinged from the left.

During the next few days there was no improvement. The patient passed no urine, 30 cc of bloody urine being obtained by catheter on the third hospital day. The fluid intake averaged 600 cc a day. The costovertebral-angle tenderness persisted, and nausea, muscular twitching and a positive Chvostek sign developed. The nonprotein nitrogen rose to 154 mg per 100 cc. On the fourth hospital day the patient expired.

DIFFERENTIAL DIAGNOSIS

DR. CHARLES L. SHORT: The first question that we must answer is, What was the nature of the original infection that apparently began three weeks before admission? This was presumably in the respiratory tract and suggests bacterial pneumonia. Perhaps we shall be helped by the x-ray films of the chest. May we see them now?

DR. STANLEY WYMAN: I do not believe that the films will be helpful. They show a large heart and a few small, indefinite linear areas of density in both bases, which, I suppose, lie in the lower lobes. I do not see frank consolidation.

DR. SHORT: Does that picture suggest infection rather than congestion?

DR. WYMAN: It is the picture one sees in atelectasis in any patient lying in bed with some impairment of diaphragmatic motion.

DR. SHORT: Does the film of the abdomen show any definite point of obstruction or rather suggest ileus?

DR. WYMAN: The film of the abdomen is more in keeping with ileus than with true intestinal obstruction.

Examination of the blood showed a hemoglobin of 14.6 gm and a white-cell count of 10,500, with 68 per cent neutrophils. The serum protein was 6.9 gm and the nonprotein nitrogen 28 mg per 100 cc., and the chloride 105 milliequiv per liter. The urine was normal.

An x-ray film disclosed a round, soft-tissue mass between the heart and the dorsal spine measuring

episodes of gastric eructations and had been on a bland diet for eight years. Apparently, he had not lost weight except when he tried to lose it. Two months before entry he had difficulty in swallowing. With this difficulty in swallowing he did not lose much weight, — only 16 pounds, — and on physical examination he was "a well nourished, heavy-set man." We believe that if a person has at least 5



FIGURE 1

about 8 cm in diameter, that caused the barium to deviate toward the right and posteriorly and spread the esophageal lumen into a flattened, semi-circular area (Fig 1). The stomach and duodenum were outlined normally. The heart and lung fields were not remarkable.

On the fourth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR LEFOY SCHALL This patient had a history of the development of midsternal pain during eating fifteen years previously, and a diagnosis of cardiovascular disease was made at that time. Was this pain really sharp pain or merely distress? Did it radiate to the back or to the shoulder? Was it relieved when he regurgitated food? Apparently it was. He had

mm of esophageal lumen he can swallow well masticated food and that so long as he can keep up fluid intake he will not have too much weight loss.

Could the symptoms presented in this case have been due to carcinoma? At the age of forty-three years, they could. Yet pain is not an early symptom of carcinoma. If there is ulceration there may be pain on swallowing. There was no history of an esophagoscopy or biopsy. The x-ray report mentions a flattened esophageal lumen, and I take it that the lumen was also deviated. I do not believe that this was carcinoma of the esophagus because the symptoms were not present long enough. Pain is unusual, — except late in the course, — and there had not been sufficient weight loss.

There was a nodule in the thyroid gland. I do not know whether this is a red herring or not,

PATHOLOGICAL DISCUSSION

DR MALLORY Autopsy showed interesting kidneys. They weighed 450 gm., and for a woman of eighty-nine that is significant hypertrophy. The surfaces were mottled and purplish red, and the capsules stripped fairly readily. When the organs were cut it was found that the entire cortex of both kidneys was infarcted, presenting the gross picture of diffuse cortical necrosis. This is seen most frequently — in about 2 out of every 3 cases, I should say — in young women during the terminal stages of pregnancy or in the first few days following delivery. At the age of eighty-nine that possibility need not be considered. Cortical necrosis has been seen in a scattered variety of other conditions and is occasionally seen in male patients.

When we examined the sections of the kidneys microscopically another possibility was brought up. In all sections there were many small arteries showing the typical changes of periarteritis nodosa. A few arteries outside the renal substance also showed the same lesion — few indeed, but some. There was a characteristic lesion in one adrenal gland, a few changes in the perirenal fat tissue, and a single lesion in the heart. Diffuse involvement of the small renal arteries with periarteritis nodosa might produce the same total infarction of the cortex that one sees in so-called "primary cortical necrosis." I think that the way in which this case should be classified remains debatable. The facts that the arterial lesions were so characteristic of what one sees in periarteritis nodosa and that at least a few lesions were found in organs other than the kidneys lead me to make periarteritis nodosa my primary diagnosis.

The other changes found were only those that one might expect to find in a very old person, — extremely severe arteriosclerosis of the aorta, with multiple ulcerated atheromas and secondary thrombi, — but the main renal arteries were not markedly involved. The heart was hypertrophied, and the lungs were emphysematous, the gall bladder was filled with small stones, and the bile ducts were patent.

DR SHORT What did the tubules show?

DR MALLORY The glomeruli and all tubules in the cortex were completely necrotic, a picture exactly like that of infarction, except that it was symmetrical and diffuse throughout the entire cortex of both organs.

DR FLETCHER H. COLBY Were you able to determine which arteries were responsible?

DR MALLORY In cases of idiopathic cortical necrosis, vascular changes are variable and inconsistent. There are usually necrosis and thrombosis within the actual areas of infarction, but vascular lesions are not found outside. Not all cases show vascular changes, so that it is difficult to attribute the cortical necrosis to a primary mechanical obstruction of the arteries. The pathogenesis of primary cortical necrosis remains a complete mystery.

DR COLBY Presumably toxic?

DR MALLORY A similar lesion has been produced in experimental animals with staphylococcus toxin, but in human beings there is rarely evidence of an infectious etiology. In this case the finger of suspicion points strongly to sulfonamide sensitivity. It is interesting, however, that no trace of persisting sulfonamide, either free or acetylated, could be found in the blood plasma.

REFERENCES

1. Rich, A. R. Role of hypersensitivity in periarteritis nodosa as indicated by 7 cases developing during serum sickness and sulfonamide therapy. *Bull. Johns Hopkins Hosp.* 71: 123-140, 1942.
2. *Idem*. Additional evidence of role of hypersensitivity in etiology of periarteritis nodosa: another case associated with sulfonamide reaction. *Bull. Johns Hopkins Hosp.* 71: 375-379, 1942.
3. Cushny, A. R. *Pharmacology and Therapeutics*. Thirteenth edition. Revised by A. Grollman and D. Slaughter. 868 pp. Philadelphia: Lea & Febiger, 1947. P. 736.

CASE 33182

PRESENTATION OF CASE

A forty-three-year-old Jesuit brother entered the hospital because of midsternal pain during eating.

Fifteen years before entry the patient had begun to have midsternal pain that occurred during eating and was relieved when he ceased to eat. An x-ray film was taken at that time, and he was told that he had spasm of the esophagus. Subsequently, he began to have episodes of gaseous eructation and epigastric distress. Seven years later he had been put on a bland diet, which he had continued to follow ever since. Nevertheless, the symptoms continued essentially as before. In addition, he had intermittent bouts of diarrhea with left-sided and lower abdominal cramps. There had been no melena. Two months before entry the patient began to have difficulty in swallowing. When he tried to force food down he developed a severe pain in the right side of the chest. On two occasions he regurgitated undigested food. A month before entry he became unable to belch — such eructation had previously given him some relief. An x-ray film was stated to have revealed "a tumor" in the esophagus. The patient had lost 16 pounds during the year before entry, during which he had been making conscious efforts at weight reduction by means of dietary restrictions. The only other complaint was intermittent pain in the right knee radiating up and down the leg and occurring after protracted standing.

Physical examination revealed a well nourished, heavy-set man. A firm nodule, 0.5 cm. in diameter, was palpable in the left lobe of the thyroid gland, and there was a similar nodule just above the isthmus. Examination of the heart and lungs was negative. There was tenderness in the epigastrium just below the xiphoid but no spasm or palpable masses. The medial aspect of the right knee was slightly tender, but motion was normal.

The temperature, pulse and respirations were normal. The blood pressure was 125 systolic, 75 diastolic.

The New England Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

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MATERIAL should be received not later than noon on Thursday, three weeks before date of publication

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THE TAFT BILL

THE Taft Bill (S. 545), which was introduced on February 10, 1947, is meeting with considerable approval and support from organized medicine. The Massachusetts Medical Society has endorsed many of the stated objectives of previously proposed national health legislation but has opposed revolutionary trends. It considers universal compulsory insurance undesirable and unnecessary, since the American public, physicians and governmental agencies are not ready for it. It believes that present progress is satisfactory and should be continued, instead of making a reckless leap into the realms of medical bureaucracy. Even if compulsory insurance eventually proves to be necessary, there should be an evolutionary change.

Organized medicine makes no claim that present medical care is adequate. It is still far short of meeting the needs of all the people. But the medical profession is trying to preserve values, and it appears that a good beginning has been made. Voluntary health insurance is rapidly expanding. The Blue Cross now has a membership approaching 30,000,000 in the Nation and about 2,000,000 in Massachusetts. The revised June contracts of the Massachusetts Blue Cross will provide comprehensive coverage of all hospital charges. The Massachusetts Blue Shield is also doing well with a membership greater than 500,000. Rapid expansion is anticipated after the adoption of the revised June schedule, which will give complete surgical and obstetric care outside the hospital, as well as medical and surgical care in the hospital. To the few in the medical profession who have thus far failed to support this voluntary insurance program, it can only be pointed out that the definite trend toward one of two schools of thought — compulsory and voluntary — will eventually necessitate a decision to co-operate.

The Taft Bill aims to preserve and foster existing agencies and to ensure the continued independence of the American people and the medical profession. Briefly, it plans to bring together all the scattered federal health activities into a single national health agency, headed by an outstanding physician. It would provide grants-in-aid to states for the extension of medical care to people unable to pay for it, amounting to \$200,000,000 a year for general surgical and medical services and to \$20,000,000 a year for dental services, the states to match these grants-in-aid on a variable basis. It aims to encourage voluntary prepayment plans and to extend federal grants to pay the subscriptions of indigents, and it allows federal employees, through individual choice, to join voluntary health-insurance plans by payroll deductions. It would determine actual medical needs by requiring state surveys financed with federal subsidies, and it would provide grants-in-aid for research, especially in neuropsychiatry and dental health. It would also require states to have periodic medical and dental examinations of school children, if the parents cannot afford such services.

but could it have been a thoracic thyroid gland? I have not yet seen the x-ray films and do not know whether the obstruction was situated high or low, but the report says that there was a round mass behind the heart that had flattened the esophagus. I doubt whether this could have been a thoracic thyroid gland.

I do not believe that the patient had cardiospasm. In cardiospasm it is the lower end of the esophagus that is involved. He had distress and regurgitation of food, but there was no substernal pain. The x-ray film may show whether or not there was a real cardiospasm with dilatation of the esophagus above.

Could this have been a mediastinal cyst? I do not believe that it was a pulsion diverticulum, which generally involves the upper end of the esophagus and is most unusual in this area. Traction diverticulum is usually due to adhesions, perhaps from the vertebrae, that pull the esophagus out. I rule out traction diverticulum of the esophagus in this area because it is usually higher.

Could this have been a new growth of the mediastinum? Dermoid tumors usually involve the anterior mediastinum. This growth was posterior, between the heart and the esophagus. Could something outside have caused pressure between the heart and the mediastinum?

There was no history of respiratory difficulty, so that, whatever the lesion, it was too low to cause pressure on the large bronchi. This area is too low for aneurysm. The mucosa appears intact, which is strong evidence against carcinoma. I shall therefore consider benign lesions of the mediastinum, among which are tuberculous lymphadenitis and Hodgkin's disease, although nothing in the history suggests tuberculosis. A gumma should also be considered, but I do not believe that it is likely.

The most probable diagnosis is a cyst of the mediastinum.

DR CHESTER M JONES: Would you include neurofibroma as a possible cause of the mass?

DR SCHALL: I do not know. A neurofibroma may be a primary tumor of the mediastinum.

DR JONES: This mass was posterior, and neurofibroma should undoubtedly be included.

DR SCHALL: Yes, let us say that Hodgkin's disease, noninfectious lymphadenitis, tuberculous lymphadenitis and gumma are all possibilities, but I am in favor of a cyst.

DR TRACY B MALLORY: Is there anything further from the x-ray point of view?

DR STANLEY WYMAN: As Dr Schall has said, the mucosa is intact. The barium has been forced into a thin shell over the mass, and the deviation is more apparent to the right. The mass appears to arise outside the mucosa of the esophagus, which is not involved. The question is, Does it arise in the esophageal wall without arising in the mucosa?

DR SCHALL: We must think of the myomatous group of tumors, if the mass arose from the wall. I do not believe that it was a lipoma, because that is pedunculated and is usually at the upper end extending down into the esophagus.

DR W WILSON SCHIER: Could a vascular tumor, such as cavernous hemangioma, have arisen there?

DR RICHARD H SWEET: I have seen only one such case. This was in a patient on whom I operated a few weeks ago. The tumor was in the superior mediastinum.

DR MALLORY: Dr Sweet, will you tell the findings at operation?

DR SWEET: There were two reasons why we made a preliminary diagnosis of intramural benign esophageal tumor in this case — without the benefit of esophagoscopy, I might add. In the first place the x-ray appearance seemed to us, and I believe to Dr Schatzki or whoever interpreted the films, to be characteristic of that type of tumor. The other reason was the nature of the symptoms. The patient really had to work hard to get anything through the esophagus. He had a good deal of discomfort, and a benign tumor or cystic tumor of the mediastinum of such relatively small size in my experience does not give dysphagia of the severity that he had or so much pain or discomfort. For these two reasons we thought that this was an intramural esophageal tumor.

The tumor lay toward the right. We exposed it on the left side of the chest and dissected it from behind the heart and from the right chest. We found that the longitudinal muscle fibers were spread out in such a way that groups of fibers were separated from one another, but by incising the muscularis, we could dissect it free. We broke into it and discovered that it was cystic. The mucosa was not involved. We were able to shell the cyst out of the wall of the esophagus and restored continuity by suturing the muscularis together.

CLINICAL DIAGNOSIS

Benign tumor of esophagus

DR SCHALL'S DIAGNOSIS

Cyst of mediastinum

ANATOMICAL DIAGNOSIS

Congenital tracheobronchial cyst of esophageal wall

PATHOLOGICAL DISCUSSION

DR MALLORY: Microscopically, sections of this cyst showed a considerable amount of inflammation and destruction of the lining epithelium over many areas, but in some spots ciliated columnar epithelium persisted, which established it as a congenital cyst of misplaced tracheobronchial epithelium. The location was not far from the spot where tracheobronchial fistulas are seen in early life.

MICHAEL ALOYSIUS TIGHE

1882-1947

Michael Aloysius Tighe was born at Meriden Connecticut, and moved to Lowell at an early age. He was a graduate of St. Patrick's Boys' School and attended St. Francis Preparatory School in Brooklyn, New York. After graduating from Boston College, where he received an A.B. degree in 1903, he entered Harvard Medical School, receiving his M.D. degree in 1908. He soon established himself in practice in Lowell and was immediately appointed to the surgical staff of St. John's Hospital, where he served for nearly forty years, being chief of the surgical staff at the time of his death. His faithful service to his patients and to the hospital can never be adequately measured.

For a number of years he held the office of city physician and was at one time associate medical examiner for the Northern Middlesex District. He had been president of the Middlesex North District Medical Society.

Early in his medical career Dr. Tighe became a councilor of the Massachusetts Medical Society. His experience on matters of general medical and public concern began about the time the Workmen's Compensation Act was passed in 1912. He believed that the Act should be amended for the general good. He visited various district societies and presented his arguments in a convincing manner and later appeared before the Legislature. The Act was amended and has since proved to be a most satisfactory piece of legislation. Subsequently he was an important figure in questions of public relations and his opinions were eagerly sought by laymen and members of the profession. He had an uncanny sense of seeing through debatable points quickly and was able to clarify muddled discussions in the form of a motion clearly and briefly stated. He was always an important member of a committee, but he never assumed a leading role unless his opinion was fortified with plainly stated facts and sound logic.

Because of his wide knowledge of subjects pertaining to the Society, he was appointed secretary in 1941, a position that he filled capably for nearly six years. Through his faithful, diligent and

efficient work he will undoubtedly be recognized as one of the outstanding secretaries of the Society, and he will always be remembered as the "war secretary." Only a man of high ideals and fine motives could have carried on so successfully through those many troublesome years and have still been held in such great esteem and respect. In addition, he believed that the Society should render more service to its fellows, and for that reason gave much needed aid and sympathetic advice to returning veterans and new members.

It was largely through his rapt devotion to his secretarial duties that he won the real affection and friendship of all members of the Society.

His clear thinking was made evident by the excellent manner in which he expressed himself, his enunciation showing care and forethought. By nature he combined gentleness with sensitiveness. He was appreciative of the finer things in life. He stood for justice and fairness, and he insisted on the truth as he saw it. In heated arguments he kept his dignity and poise and never created animosity. Indeed, he was



a cultured and scholarly gentleman.

He had traveled considerably both in this country and abroad. Besides enjoying prose and poetry, he derived a great deal of pleasure from golf — not only for the game itself but also for the companionship that it afforded. He adored his family, and the evening before his death, all members gathered at his home for the celebration of his birthday.

Dr. Tighe was a fellow of the American College of Surgeons, American Medical Association and New England Obstetrical and Gynecological Society and a member of the Harvard Club of Boston and Longmeadow Golf Club of Lowell.

He is survived by his widow, three sons, a daughter, five grandchildren and two sisters.

Impressive rites for Dr. Tighe were held at the Church of the Immaculate Conception in Lowell. The extremely large attendance by physicians from all parts of the Commonwealth, nurses, hospital executives, friends and former patients attests the high regard in which he was held.

The objective of adequate medical care is to make it available to all the people regardless of financial status. Actually the Taft Bill is designed to reach, in particular, the low-income group. This is a special need. For those who can afford it, direct payment or coverage by a voluntary prepayment plan is the responsibility of the individual. The indigent group is now taken care of, after a fashion, by local welfare agencies or private charity. Subsidy from some tax source will probably be needed to provide unusual diagnostic costs and to meet the expenses of catastrophic illness in this group.

The attainment of adequate medical care for all the people should follow an evolutionary process over a long period, with co-operation of all concerned. The Taft Bill seems to be, at least so far, the best framework on which to build the kind of health legislation that the country needs. It is to be hoped that, after conflicting groups have made the necessary compromises that are a proper mechanism for forging laws in a democracy, the foundation of a broad progressive system of medical care will be evolved. In the meantime, this bill warrants the attention and study of every physician who is interested in his own future, the future of organized medicine and the health of the people of the United States.

MAY DAY — CHILD HEALTH DAY

MAY Day, since a Congressional resolution was passed in 1928, has been traditionally Child Health Day. This year its observance is taking a slightly different form than usual. In a world over-ready for tranquillity but overaccustomed to violence, the current May Day will call attention to the fact that accident, not disease, is now the leading cause of death among children. In the interest of accident prevention in the home, the Children's Bureau set aside the week of April 27 in which to conduct a nationwide educational campaign.

Accidents, according to available statistics, now annually take the lives of nearly twenty thousand boys and girls under twenty years of age, and many more thousands are injured and crippled. Most of these accidents are preventable. In 1944, six thousand children under five years of age died from injuries sustained at home. Of these, two thousand died of burns, and thirteen hundred as a result of mechanical suffocation. Human carelessness, as a killer, is taking the place of pneumonia, enteritis, measles, diphtheria, meningitis, poliomyelitis, whooping cough and scarlet fever combined, many of these diseases, as a result of human intelligence effectively applied, are losing much of their terror.

Nothing can be done about the lives that have been lost from accident except to make their numbers stand as a grim reminder of the carelessness with which we live, and a warning that we must devote ourselves to attaining a better record for the future. Much can be done for the uncounted thousands who have survived their injuries and still live on as more or less permanent cripples.

Many of these patients are treated under the federal-state crippled children's program, administered by the states and financed largely with federal funds, and more would be cared for if those who need the help could be found. This seems to be one of the present problems, — to find the patient, — since the family frequently does not know of the aid that can be obtained without charge and without regard to financial circumstances.

The fact that accidents are now the leading cause of death among children does not mean that the death rate from accidents has actually risen. What it does mean is that science has been able to effect a decline in the death rate from disease. That decline has not been paralleled in accident prevention by the use of ordinary common sense and an acceptance of responsibility for the welfare of those who still require protection and guidance.

is outside. The ureters do not enter the bladder at all, but make their exit above the brim of the pelvis on either side. The glans is all that indicates the existence of the penis, and projects out from the place where nature intended that organ should be located. An opinion has been given that the bones are not united in the usual manner in front, but are tied imperfectly together by the intervention of a ligamentous band. It strikes us that an effort should be made to lessen this poor wandering boy's sad calamity. If some benevolent gentleman would give him the use of a free bed awhile at the Massachusetts General Hospital,* our unbounded confidence in the ingenuity and skill of the surgeons of that institution, leads us to believe that he might there find at least some relief. — Tuesday, 3rd inst., being the concluding day of the courses, Dr. Warren gave his last lecture to the Medical School. He took leave of his audience, by wishing for his students a continued zeal in the prosecution of their studies, for the candidates for graduation a triumphant passage through the narrow gate that leads to professional honors, and for the young practitioners abundant opportunities of relieving the poor and, adequate reward of their labors from the rich, and, above all, a conscientious discharge of their duties through life. — At the meeting after the close of the exercises, Dr. C. T. Jackson was called upon by Dr. Bigelow to speak in regard to the insensibility to pain produced by inhalation of sulphuric ether vapor. Dr. Jackson would only re-assert that he discovered that insensibility to pain was produced by such inhalations and that he communicated the fact to one of his pupils in February, 1846, and requested him to try the experiment when he had a tooth extracted. He regretted that any misunderstanding should have arisen concerning the discovery. He was willing to allow great credit to others for their enterprise and zeal in promoting its introduction, and for skill in improving his originally simple apparatus. Yet it would certainly be unwarrantable for the miner, who carried Davy's safety lamp into the fire damps of a mine, to dispute the claims of its original inventor, for he received that instrument already proved to be efficient, with the assurance that it would guide him in safety amid the explosive gases of the mine. — Extracted from the *Boston Medical and Surgical Journal*, March, 1847.

R F

*The records of the Massachusetts General Hospital reveal that in January, 1846, J. H., nineteen years old, was admitted to the Surgical Service for congenital malformation of the urinary organs and was discharged unrelieved.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

SMALLPOX PROGRAM FOR MASSACHUSETTS

The appearance of 8 cases of smallpox in New York City recently, with a total of 2 deaths, has

given rise to considerable and unwarranted concern. The fear that this disease may attain even larger epidemic proportions has been recently aggravated by the misinterpretation of a radio report of a small-pox outbreak within an institution.

There has been no reported case of smallpox within Massachusetts for the past fifteen years. In the event of the occurrence of this disease within Massachusetts, a program has been formulated for the care and treatment of such cases. If the diagnosis of smallpox is suspected in any one case, it is imperative that the state or local health department be notified immediately.

The Biologic Laboratory of the Massachusetts Department of Public Health has on hand sufficient vaccine to satisfy requests at a normal demand level. Personnel from other divisions of the Department of Public Health is being diverted to assist in the present work of increasing the present supply of smallpox vaccine. Physicians are cautioned, however, that in the event of a panic concerning the New York epidemic, the demand for vaccine will far exceed the supply.

To clarify the status of smallpox in Massachusetts, a conference of public-health officials representing the Massachusetts Department of Public Health and the Boston Health Department was called, and the following recommendations were adopted:

- No mass vaccination of the general public is indicated.
- Priority for use of the present supply of vaccine shall be restricted in the following order:
 - (a) To actual contacts of cases.
 - (b) To physicians, nurses and hospital personnel.
 - (c) To unvaccinated persons traveling to areas of small-pox prevalence.
 - (d) To infants six to twelve months of age and for re-vaccination of preschool children prior to entering school.

The above information has been forwarded to all hospitals, medical societies and boards of health within the Commonwealth.

DIAGNOSTIC TESTS FOR CERTAIN VIRUS DISEASES

For the present the Department has available, through a co-operative arrangement with Harvard Medical School, facilities for making a limited number of serologic tests for Influenza A and B by the red-cell agglutination inhibition technic, for mumps, psittacosis and lymphogranuloma venereum by complement-fixation tests and for lymphocytic choriomeningitis by neutralization tests.

Specimens should be submitted in the Department's special outfit and accompanied by properly filled out forms entitled "Request for Serological Tests for Certain Virus Diseases." The special outfit to be used, which is the same as the Department's undulant-fever outfit, and the special forms to be filled out may be obtained from local boards

MASSACHUSETTS MEDICAL SOCIETY

BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of dates can be avoided.

ANNUAL GOLF TOURNAMENT

The annual golf tournament of the Massachusetts Medical Society will be held at the Woodland Golf Club, 1897 Washington Street, Newton, commencing at 1 00 p m on Tuesday, May 20. Prizes for low gross and net scores will be awarded, as well as the Burrage Bowl, emblematic of the championship of the Society.

Dr Henry W Godfrey has been appointed chairman of the Golf Committee, and entries should be sent to him at 14 Hancock Street, Newton. Post entries are allowed.

There will be an opportunity to have dinner at the club for those who desire it.

SIDNEY C WIGGIN, *Chairman*
Committee on Arrangements

DEATHS

PERKINS — George E Perkins, M D, of Belmont, died April 3. He was in his seventieth year.

Dr Perkins received his degree from Georgia College of Eclectic Medicine and Surgery in 1913. He was a fellow of the American Medical Association. He was a member of the staffs of the Boston Dispensary and the Massachusetts Memorial Hospitals and was acting director of the Division of Venereal Diseases, Massachusetts Department of Public Health.

His widow survives.

STONE — Henry E Stone, M D, of Boston, died March 31. He was in his fifty-sixth year.

Dr Stone received his degree from Tufts College Medical School in 1912.

His widow and a son, Dr Nathaniel M Stone, survive.

A HUNDRED YEARS AGO

As they threatened, the Physicians of Berkshire County have petitioned the Great and General Court of Massachusetts for new legislation concerning the Massachusetts Medical Society. At present, they claim, its meetings, its funds and its library are confined in Boston, at the eastern extremity of the Commonwealth so that the portion of the profession residing in the *opposite extremity* can derive little or no benefit from either. They ask that the State Medical Society may be so re-organized that a participation of the funds and library already accumulated may be secured to County Medical Societies or that the County of Berkshire may be constituted a separate and distinct medical society, clothed with

the usual powers and privileges pertaining to such bodies — The Counsellors of the Massachusetts Medical Society deprecate this action. It can be shown, they say, that more property has been given by the parent Society to the County of Berkshire than the whole amount of assessments ever received by the Society from them. The library of the Society is a small collection of old books, the result entirely of donations and legacies. It is but little used in Boston, and by a regulation of the Society, any District Society may carry off sixty volumes at a time for the use of its members. Of this privilege the County of Berkshire has freely availed itself. If by "the usual powers and privileges" of medical corporations, it is intended to include the power of conferring *licenses to practice physic*, this power becomes dangerous and liable to abuse. If such a power is granted to the physicians of Berkshire, there is no reason why the physicians of any other county in the Commonwealth may not claim the like privilege. And thus the State might be cut up into small and irresponsible tribunals, disposing of licenses for a pecuniary compensation, and not accounting to any higher authority for abuse — which might result from the misuse of their privileges — An exhibition of extraordinary interest to humanity occurred at the Massachusetts General Hospital on Saturday last. A patient was presented who, we understand, was laboring under paraplegia, having its origin in a caries of the lower dorsal vertebra, and for which Dr Warren proposed the actual cautery. After the patient had inhaled the letheon, Dr Warren run an iron rod, heated to a white heat, to the length of about two feet, up and down the back, each side of the spine, burning two lines on one side and one on the other, and then carried it zigzag across, between the spinous processes, the same distance. The patient during this process was wholly unconscious of pain, under the severest test to which he could be subjected — that of a hot iron applied to the naked skin — Dr Ames of Wayland, Mass., in forty-one operations drew from a lady in that town, who died not long since, *fourteen hundred pounds of water!* On one or two occasions two pailsful of fluid were taken away at the same time. The lady, immediately after each operation, till towards the close of life, was so completely relieved that she at once assumed the management of her domestic duties. There may have been more remarkable cases on medical record, but nothing, we believe, more striking has occurred in this region — A young native of Chester, Vt., J H, 19 years old, who is maintained chiefly by the benevolent contributions of medical gentlemen, on whom he calls while travelling over the country, exhibits in his person, one of the most extraordinary and inconvenient malformations imaginable. In the first place there is only a portion of a bladder, about the size of a hen's egg, and that inverted — and instead of being within the cavity of the abdomen, it

Women in Industry. Their health and efficiency. By Anna M. Baetjer, Sc.D. Issued under the auspices of the Division of Medical Sciences and the Division of Engineering and Industrial Research, National Research Council. Prepared in the Army Industrial Hygiene Laboratory. 8°, cloth, 344 pp., with 122 tables. Philadelphia and London W B Saunders Company, 1946.

This study was made during World War II for the purpose of ascertaining the utilization of womanpower in industry to further the war effort. An exhaustive critical review was made of the literature to determine whether such utilization had a sound physiologic basis. The material is well documented with graphs and statistical tables. The text is divided into main sections, comprising seventeen chapters, and four appendixes, as well as a bibliography of twenty-two pages. The sections deal with the following aspects of the subject: the physique of women in relation to work, fatigue and physical stress, absenteeism due to sickness, accidental injuries, occupational diseases, gynecologic and obstetric problems and mortality and fertility in relation to occupation.

This monograph presents information about the ability of women to perform operations previously considered suitable for men only and also gives a clear picture of the facts known about the relation of employment to the health of women. It is not the intention to justify the employment of women in industry but to make available valuable information for the proper job placement of women when their service is required. The study endeavors to present the scientific facts known concerning the health and efficiency of women in relation to their employment on the basis of the literature and the information gained during the war, and to indicate phases of the problem requiring further investigation, to obtain maximum health and working efficiency. Section seven is devoted to a summary and lengthy conclusions in which each main section is treated separately and all pertinent facts relative to each are analyzed. The appendixes comprise valuable collateral information, including a table showing the distribution of gainfully employed women according to occupational classes and industrial groups as shown by the 1940 United States Census, a list of occupations suitable for women and a summary of state labor laws for women as of 1944. In addition to the main bibliography, selected references are appended to each chapter.

The material is well organized, and the text well printed on good paper. This monograph should be in all medical libraries and should prove valuable to all industrial physicians.

Water Treatment and Purification. By William J. Ryan, M.E. Second edition. 8°, cloth, 270 pp., with 66 illustrations. New York and London McGraw-Hill Book Company Incorporated, 1946. \$2.75.

This manual, first published in 1937, has been revised to include descriptions of processes that have come into use since the issue of the first edition. These include organic ion exchange, materials for water softening, acid absorbents, demineralization, the treatment of boiler water to prevent embrittlement, new equipment for accelerating the lime-and-soda ash softening process, new developments in the use of chlorine for sterilization and the stabilization of water to prevent scale deposits.

Although this manual has been written primarily for engineers and others concerned with water purification, it should prove useful to all persons interested in pure water and water supply. The chapters on impurities, sedimentation and coagulation, filtration and water analysis are of public-health interest. The material is well organized, well written and printed with a good readable type on good paper. The manual is recommended for reference purposes.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Three Unpublished Drawings of the Anatomy of the Human Ear. By the late Max Brödel with the assistance of P. D. Malone, Stacy R. Guild and S. J. Crowe. 4°, cloth 9 pp.

with 4 illustrations and frontispiece. Philadelphia W B Saunders Company, 1946. No charge.

Max Brödel, 1870-1941, pioneer medical artist, long connected with the Johns Hopkins University School of Medicine, is honored in this publication by the W B Saunders Company. These unpublished drawings are excellent examples of the high quality of work executed by Brödel, and are thoroughly characteristic of his style. They are presented to the medical profession as a tribute to the memory of a great artist in his chosen field.

The Normal Electroencephalogram. By Leo M. Davidoff, M.D., professor of clinical neurological surgery, Columbia University College of Physicians and Surgeons, and attending neurologic surgeon, Montefiore Hospital, New York City, and Cornelius G. Dyke, M.D. Second edition, thoroughly revised. 8°, cloth, 252 pp., with 155 illustrations. Philadelphia Lea and Febiger, 1946. \$5.50.

This second edition of a standard monograph has been revised on the basis of an accumulation of over eight thousand electroencephalograms, more than double the number available for the first edition. The text is well printed with a good type, and the illustrations are excellent. The book is recommended to all medical libraries and to neurologists and physicians interested in the subject.

Exercises in Electrocardiographic Interpretation. By Louis N. Katz, M.D., director of cardiovascular research, Michael Reese Hospital, Chicago, and professorial lecturer in physiology, University of Chicago School of Medicine. Second edition, thoroughly revised. 4°, cloth, 288 pp., with 141 illustrations. Philadelphia Lea and Febiger, 1946. \$6.00.

This manual, a companion volume to the author's large work on the same subject, has been revised to conform to the advances in electrocardiography. The total number of cases has been increased to one hundred, and thirty-eight have been discarded and new ones substituted. The descriptions and interpretations of the other cases have been revised to conform to the newer terminology of the subject. The work is written for persons requiring practice in reading unknown electrocardiograms. The book is well published in every way and should prove valuable to students of the subject.

Clinical Electrocardiography. By David Scherf, M.D., associate professor of medicine, New York Medical College, Flower and Fifth Avenue Hospitals, and Linn J. Boyd, M.D., professor of medicine, New York Medical College, Flower and Fifth Avenue Hospitals. Second edition. 4°, cloth, 267 pp., with 243 illustrations. Philadelphia J B Lippincott Company, 1946. \$8.00.

This second edition of a standard work has been thoroughly revised by the addition of new material. Some sections have been completely revised, whereas others have been expanded. Extensive bibliographies are appended to each part. The text is well printed in a two-column format.

Urologic Roentgenology. By Miley B. Wesson, M.D. Second edition, thoroughly revised. 8°, cloth, 259 pp., with 258 illustrations. Philadelphia Lea and Febiger, 1946. \$5.50.

In this new edition of a standard work, the text has been practically rewritten, and the literature brought up to date. Many of the illustrations have been deleted, and new ones substituted. The purpose of the book is to provide a manual for beginners in the field of urography. The first chapter furnishes a short history of the subject. The material is well organized, and the text is well printed with a good readable type. The book should prove useful to physicians interested in the subject.

A Primer for Diabetic Patients. An outline of treatment for diabetes with diet, insulin and protamine-zinc insulin, including directions and charts for the use of physicians in planning diet prescriptions. By Russell M. Wilder, M.D., Ph.D., professor and chief, Department of Medicine, Mayo Foundation, University of Minnesota, and senior consultant, Division of Medicine, Mayo Clinic. Eighth edition, reset. 18° cloth, 192 pp., with 8 illustrations. Philadelphia and London W B Saunders Company, 1946. \$1.75.

This standard manual for diabetic patients, first published in 1921, has been slightly revised to conform to minor

of health or directly from the State Diagnostic Laboratory, 281 South Street, Jamaica Plain 30

In each suspected case, two aseptically collected 4-cc serum specimens are required, the first taken as soon as possible after the onset of the disease, and the second ten to fourteen days later (four to five weeks later in cases of lymphocytic choriomeningitis). If facilities for separation of serum are not available, 10 cc of clotted blood for each specimen may be substituted if it is mailed to the laboratory at once. *Since positive diagnosis can be made only if a rise in antibody titer is demonstrated during the course of the illness, two specimens must be sent.* Tests for diagnosis, therefore, will be run only on paired specimens. If information regarding past mumps infection and consequent immunity alone is desired, however, only one specimen need be submitted.

For information regarding serologic diagnosis of other virus infections, the State Diagnostic Laboratory, 281 South Street, Jamaica Plain 30 (telephone, ARNold 5440), should be consulted directly.

It should be noted that none of these tests will assist in the confirmation of a diagnosis during the early acute stage. They are useful mainly in making a diagnosis in retrospect.

If intelligent selection is exercised by physicians in sending in specimens, this service may be made permanent by the Department. Because funds are limited for reimbursing Harvard Medical School for the tests, the service will have to be discontinued if lack of selection results in too large a volume of tests.

NEW APPOINTMENTS

Mary E. Spencer, Ph.D., nationally known health educator and author of several books, has been appointed chief of the Bureau of Health Information of the Massachusetts Department of Public Health. Dr. Spencer is well known in Washington circles for her work as director of the Health Education Bureau of the National Welfare Conference, in which position she represented the United States at the World Federation of Education Association at Geneva. She also served on the Hoover White House Conference on Child Health and Protection. Prior to her appointment, Dr. Spencer held the position of director of health education in the schools of Malden. She is professor of public health at Wellesley College Graduate School of Hygiene. She is vice president of the Massachusetts Public Health Association, chairman of health and nutrition of the American Association for Health, Physical Education and Recreation and a former president of the New England Health Education Association. She is the author of the textbooks *Health Education for Teachers* and *Health Through the School Day*, as well as numerous professional articles.

Eugene R. Sullivan, M.D., has been appointed assistant director in the Division of Biologic Labora-

tories, Massachusetts Department of Public Health. Dr. Sullivan, recently a lieutenant colonel in the Army Medical Corps, served three years overseas as chief of laboratories, Sixth General Hospital, consultant on blood and blood transfusions for the North African and Mediterranean theaters of operations and a member of a board for the study of the treatment of the seriously wounded. Prior to his Army service, Dr. Sullivan held positions at Harvard Medical School, Massachusetts General Hospital and Michigan University School of Public Health, working in the fields of internal medicine, infectious disease and laboratory sciences.

Martha Howard Fales, B.A., formerly dental health consultant, Michigan Department of Health, has joined the staff of the Massachusetts Department of Public Health, Division of Dental Health, as public-health dental-hygiene supervisor.

Julian M. Karasoff, D.V.M., has been appointed veterinary food inspector in the Division of Food and Drugs, Massachusetts Department of Public Health. Prior to his appointment, Dr. Karasoff practiced privately as a veterinarian. He also served as slaughtering inspector in Waltham.

Salvatore R. Traina, M.D., formerly command surgeon, Seventh Air Service Area Command in Tokyo, is now serving as physician in charge of the mobile unit of the State Blood Donor Program, Division of Biologic Laboratories, Massachusetts Department of Public Health. Prior to his appointment, Dr. Traina served for twenty-eight months in the Asiatic-Pacific Theater, being discharged with the rank of major in the Medical Corps. He is a diplomate of the National Board of Medical Examiners.

Barbara Ford Carter, M.D., has been appointed assistant district health officer of the North Metropolitan District, Massachusetts Department of Public Health. Dr. Carter was formerly house officer and assistant resident, Third Medical Service, Boston City Hospital.

BOOK REVIEWS

Fees and Fee Bills. Some economic aspects of medical practice in nineteenth century America. By George Rosen, M.D., Ph.D. 4°, paper, 91 pp. Baltimore: Johns Hopkins Press, 1946. \$1.50.

Dr. Rosen in this monograph has made a valuable contribution to the medical economic history of the United States. He has published a number of fee tables from various sections of the country and has shown the gradual changes of professional fees from 1815 to 1891. The fee bill of the Boston Medical Association of 1864 is reproduced from the *Boston Medical and Surgical Journal* of the same year.

It is not generally known that the Boston Medical Association was established for the sole purpose of regulating the fees of physicians and the ethics of the profession. It was formed in 1806 and became extinct in 1910. It published from time to time, beginning in 1808, fee tables and a pamphlet called *Medical Police*, in which ethics and fees were discussed. Its records are now in the Boston Medical Library.

This monograph loses some of its value because of the lack of an index. At least a list of the fee tables should have been published. It should find a place in all medical-history collections, however, as well as in business libraries.

The New England Journal of Medicine

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Volume 236

MAY 8, 1947

Number 19

BENIGN AND MALIGNANT TUMORS OF THE SMALL INTESTINE*

THOMAS W. BOTSFORD, M.D.,[†] AND ROY E. SEIBEL, M.D.[‡]

BOSTON

THE small intestine comprises the longest portion of the alimentary canal and yet receives small consideration in the diagnosis of intestinal tumors. The reason is the rarity of neoplasms in the small bowel. Such easy setting aside is in line with the attitude toward these tumors in general and can no longer be tolerated by the profession. Moreover, tumors of the small intestine are possibly curable in the early stages, and certainly the small bowel is heir to a variety of benign tumors that may cause symptoms. The diagnosis of the lesions is usually obscure, and until the physician entertains the possibility, it will remain obscure.

It is the purpose of this communication to stress factors that may aid in the early diagnosis of small-bowel tumors and to review the primary cases seen at the Peter Bent Brigham Hospital. X-ray diagnosis of these tumors is especially emphasized. The material for this report was obtained from the clinical and autopsy records of the hospital from 1913 to 1946. Only histologically verified benign and malignant primary tumors of the duodenum, jejunum and ileum are included. Carcinomas of the head of the pancreas and of the ampulla of Vater are not considered. Several cases in the present series have previously been reported. Oughterson and Cheever¹ and Botsford and Newton² each reported a case of submucous lipoma of the ileum, and Newton and Buckley³ reported one of carcinoma of the jejunum. In 1934 Baile⁴ included 8 instances of argentaffinoma of the jejunum and ileum in his exhaustive study.

A total of 65 cases of primary small-bowel tumor were found, and in 33 of these the tumors were malignant. Shallow, Eger and Carty⁵ state that primary cancer of the small intestine occurs in 0.1 per cent of all cases in which autopsies are performed and is thirty-six times less frequent than malignant tumors of the colon, but that 60 per cent of intestinal sarcomas are located in

the small bowel. Horslev,⁶ however, was able to collect 243 cases of carcinoma of the jejunum and ileum from the literature between 1932 and 1941, it is of interest that in 7 cases the lesions were primary in a Meckel's diverticulum. Benign tumors of the small bowel are also rare, but are probably more frequent than is realized, since they seldom cause symptoms.

TYPES OF TUMOR

The types and location of the tumors are presented in Table 1. Adenocarcinoma was the most frequent tumor, occurring about equally throughout the small intestine, although the percentage localization based on length of bowel indicated a greater incidence in the upper part of the small intestine. Argentaffinoma constituted the next most frequent group, but these tumors were invasive in only 2 cases. Lymphosarcoma, next to adenocarcinoma, was the largest malignant group of clinical significance. The benign tumors—submucous lipoma, adenoma, leiomyoma and fibroma—comprised about a fourth of the whole series and were the cause of symptoms in only 3 cases. Rankin and Newell⁷ reported a higher incidence of symptoms due to benign lesions but did not include argentaffinomas in their series. In 32 cases in our series, in all of which the tumors were benign except for 1 case with a locally invasive argentaffin tumor and 2 with small carcinomas of the duodenum, the lesions were incidental findings at autopsy. A careful review of the corresponding clinical records showed no evidence of their having caused symptoms. Raiford⁸ reported 60 per cent benign lesions and 40 per cent malignant tumors in his series and pointed out that 49 per cent were incidental findings. In our series, the ileum, where lymphosarcomas and argentaffinomas characteristically occur, was the most frequent portion of the small intestine involved. There were 38 men and 27 women. The maximum incidence was in the sixth and seventh decades, but in 10 cases the malignant tumors occurred in pa-

*From the Surgical Clinic of the Peter Bent Brigham Hospital.
[†]Instructor in surgery, Harvard Medical School; associate in surgery, Peter Bent Brigham Hospital.
[‡]Formerly resident in radiology, Peter Bent Brigham Hospital.

changes in procedure developed since 1941, the date of the seventh edition. The text is written in a practical, non-theoretical manner and is based on the instruction given in the Diabetic School at the Mayo Clinic and on thousands of cases. The material is well organized and well written in plain language. The topics covered include urine testing, administration of insulin, complications, including gangrene, diet and foods.

Wm Beaumont's Formative Years. Two early notebooks, 1811-1821. With annotations and an introductory essay by Genevieve Miller, M.A., Institute of the History of Medicine, Johns Hopkins University. 8°, cloth, 87 pp., with 21 illustrations. New York: Henry Schuman, 1946. \$6.00.

Miss Miller has written an interesting introduction and has provided copious explanatory notes to this reproduction of the two notebooks of Beaumont—one medical and the other general—owned by the Washington University School of Medicine, St. Louis. The first notebook contains excerpts from medical authors, case histories, prescriptions and notes on military medicine. The second contains literary excerpts, including poetry, and war and travel diaries. The book is a credit to the publisher. It is beautiful in conception and should be in all medical libraries and medical-history collections.

New Aspects of John and William Hunter. I. Everard Home and the Destruction of the John Hunter Manuscripts. II. William Hunter and His Contemporaries. By Jane M. Oppenheimer, Bryn Mawr College. With a foreword by Fenwick Beekman, M.D. 8°, cloth, 188 pp. New York: Henry Schuman, 1946. \$6.00.

In these studies Miss Oppenheimer has made a valuable contribution to medical history. In Part I she made a new investigation and a reinterpretation of the destruction of John Hunter's manuscripts by his brother-in-law, Sir Everard Home, based on an analysis of the personal relations existing between Home, Hunter and William Clift. Part II is devoted to an evaluation of the personality of William Hunter, the great obstetrician, as revealed by his friendships with outstanding personages of his time. Likewise, the author discusses his disputes with his famous brother John. Copious notes and bibliographies are appended to both parts. The book is recommended for all medical-history collections.

Paragon Supplement. By Mead Johnson and Company. 8°, paper, 33 pp. Evansville, Indiana: Mead Johnson and Company, 1946. Sent on request.

This pamphlet is a bibliography of art techniques in various mediums especially selected for the physician artist. In addition there are a number of short papers written for the beginner by the officers of the American Physicians' Art Association. The material should prove valuable to all physicians interested in the various aspects of art.

NOTICES

REUNION AT SPRINGFIELD HOSPITAL

A combined reunion of former interns and graduates of the nursing school will be held at the Springfield Hospital on Saturday, May 17. The program will consist of operations and clinics by the medical staff and demonstrations and talks in the classrooms of the Nurses' Residence by the nursing department in the morning. At noon the unveiling of the World War II Memorial will take place in the main lobby of the hospital, following which luncheon will be served in the cafeteria to all the hospital group. The afternoon will be free for visiting and a tea in the living room of the Nurses' Residence, and the reunion dinner will be held at the Hotel Kimball at 7:00 p.m.

MASSACHUSETTS SOCIETY OF EXAMINING PHYSICIANS

The fortieth anniversary meeting and dinner of the Massachusetts Society of Examining Physicians will be held on Wednesday, May 7, at 6:30 p.m., in the State Suite of the Copley-Plaza Hotel, Boston. Dr. James C. White, chief of the Neurosurgical Service, Massachusetts General Hospital, will be the guest speaker and present a paper, illustrated by lantern slides, on the topic "The Contributions of Neuro-

surgery to Problems of Vascular Disease and Visceral Pain." Members of the Society will participate in the discussion, which will be opened by Dr. Charles A. Robinson. Reservations for the dinner may be made with the assistant secretary, Miss Anne Rodman, 157 Fourth Street, Medford, Massachusetts.

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

30 Bennet Street, Boston

Lecture Hall, 9-10 a.m.

MEDICAL CONFERENCE PROGRAM

Wednesday, May 7—Heparin Therapy of Thromboembolic Disease. Dr. Arnold Starr.

Friday, May 9—Methemoglobinemia and Sulfhemoglobinemia. Dr. C. A. Finch.

Wednesday, May 14—Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon.

Friday, May 16—The Control of Acidic-Fluid Formation in Hepatic Cirrhosis by Albumin, Mechanisms of Albumin Action in Water and Sodium Balance of Other Diseases. Dr. S. Howard Armsirong.

Wednesday, May 21—Porphyria. Dr. Marvin Bloom.

Friday, May 23—The Systemic Manifestations of Rheumatoid Arthritis. Dr. Walter Bauer.

Wednesday, May 28—Clinicopathological Conference. Drs. Richard Chute and H. E. MacMahon.

Friday, May 30—Holiday.

On Tuesday and Thursday mornings, Dr. S. J. Thannhauser will give medical clinics on hospital cases. On Saturday mornings, clinics will be given by Dr. William Dameshek. Medical rounds are conducted each weekday by members of the staff from 12:00 to 1:00 in the Lecture Hall.

All exercises are open to the medical profession.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING

THURSDAY, MAY 8

FRIDAY, MAY 9

*9:00-10:00 a.m. Methemoglobinemia and Sulfhemoglobinemia. Dr. C. A. Finch. Joseph H. Pratt Diagnostic Hospital.

*10:00 a.m.-12:00 p.m. Medical Staff Rounds. Peter Bent Brigham Hospital.

12:00 p.m.-1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

MONDAY, MAY 12

*12:15-1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, MAY 13

12:00 p.m.-1:00 p.m. Dermatological Service, Grand Rounds. Amphitheater. Dowling Building. Boston City Hospital.

*12:15-1:15 p.m. Clinicoradiological Conference. Peter Bent Brigham Hospital.

WEDNESDAY, MAY 14

*9:00-10:00 a.m. Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon. Joseph H. Pratt Diagnostic Hospital.

*11:00 a.m.-12:00 p.m. Medical Clinic. Amphitheater. Children's Hospital.

*12:00 p.m. Clinicopathological Conference (Children's Hospital). Amphitheater. Peter Bent Brigham Hospital.

*2:00-3:00 p.m. Combined Clinic by the Medical Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

*Open to the medical profession.

April 26-May 4. Industrial Health Meetings. Page 456, issue of March 20.

May 6. Greater Boston Medical Society. Page 610, issue of April 17.

May 7. Massachusetts Society of Examining Physicians. Notice above.

May 7-28. Joseph H. Pratt Diagnostic Hospital. Medical Conference Program. Notice above.

May 8. Cerebral Hemorrhage. Dr. Raymond Adams. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

May 9. Boston University School of Medicine Alumni Association. Page 554, issue of April 10.

May 9. Tuberculosis Institute. Page 646, issue of April 24.

May 12. Phi Delta Epsilon Lecture. Page 646, issue of April 24.

May 17. Reunion at Springfield Hospital. Notice above.

May 19-22. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

May 20-22. Massachusetts Physicians' Art Association. Page 340, issue of February 27.

June 5-8. American College of Chest Physicians. Page 418, issue of March 13.

June 7 and 8. American Society for the Study of Sterility. Page 504, issue of February 20.

(Notices continued on page xix)

or initiate intussusception. None of the tumors in the 5 cases in this series were the cause of any difficulty. One carcinoma of the duodenum arose in an adenoma.

Fibroma

Two cases of small pedunculated fibroma of the small bowel were encountered as incidental findings. They may cause the same difficulties as leiomyomas.



FIGURE 1 *Adenocarcinoma of the Jejunum*

The photograph of the gross specimen shows a typical annular tumor. Note the dilated proximal portion of the intestine. This tumor was not palpable preoperatively. With the lumen of the bowel opened, the small size of the tumor is more apparent.

Leiomyoma

There were only two leiomyomas, both of which were incidentally found as sessile tumors measuring a few millimeters in diameter. The lesions rarely cause intussusception or undergo sarcomatous degeneration.

SYMPTOMATOLOGY

All observers are agreed that no characteristic clinical picture is associated with benign or malignant tumors of the small intestine. The symptoms due to these lesions, however, are those either of obstruction or of bleeding into the alimentary canal with the development of secondary anemia. The

tients between thirty-five and forty-five years of age. It follows that the majority of small-bowel tumors that cause symptoms are malignant and that about a third of these are seen in patients under fifty years of age.

Carcinoma

Adenocarcinoma is the usual type encountered,⁹ and in our series all the lesions in this group were adenocarcinomas. One tumor of the duodenum arose in an ulcer, and another in the same location

Argentaffinoma

Argentaffin tumors, or carcinoids, arise from the Kultschitzky cells in the depths of the mucosal glands. They are characteristically located in the vermiform appendix and less frequently in the terminal ileum, but are occasionally seen in the stomach, jejunum and cecum. They are usually regarded as benign tumors, but occasionally they become malignant, with local invasion and distant metastases. They grow slowly in contradistinction

TABLE 1 Types of Tumor in 65 Cases

Lesion	Location			Cause of Symptoms	Incidental Finding
	Duodenum	Jejunum	Ileum		
Adenocarcinoma	6	7	5	16	2
Argentaffinoma	0	1	15	1	15
Lymphosarcoma	0	1	12	13	0
Submucous lipoma	1	1	7	3	-6
Adenoma	3	2	0	0	5
Leiomyoma	0	1	1	0	2
Fibroma	0	1	1	0	2
Totals	10	14	41	33	32

arose in an adenomatous polyp. Metastasis to the regional lymph nodes, which occurs early, was grossly present in all but 2 cases at the time of operation or autopsy. It is of special interest that duodenal adenocarcinomas were incidental findings in 2 patients with carcinoma elsewhere in the gastrointestinal tract. The stomach was involved in one patient, and the sigmoid in the other, those lesions being the cause of the symptomatology and the reasons for hospitalization. The typical adenocarcinoma of the small bowel gives an annular constriction to the intestine and is not a large tumor (Fig 1). Distant metastases are frequent late in the course of the disease.

Lymphosarcoma

Lymphosarcoma, which originates in the lymphoid tissue of the bowel wall, generally occurs in the ileum, and the mesenteric lymph nodes are involved early. The lesion is usually diffusely infiltrating and not confined to a small area of the intestine (Fig 2). Because of this, a mass is frequently palpated, in 11 of our patients with lymphosarcoma there was a palpable mass, whereas in only 2 patients with adenocarcinoma was such a mass present. It is of more than academic interest to repeat that most of these tumors were seen in the fourth decade of life.

In this study, lymphosarcoma of origin in the bowel wall was carefully separated from lymphosarcoma or lymphoma originating in the mesenteric lymph nodes. The latter rarely invades the bowel wall, although intestinal symptoms may arise from mechanical causes.

to lymphosarcoma and carcinoma, and radical resection is indicated even in the presence of distant metastases. Four patients had from two to nine multiple tumors. The usual carcinoid is seen at autopsy as a small nodule with a distinctive yellowish color.

There were two malignant carcinoids in our series, both of which have been described by Bailey.⁴ One was found to be invading the mesentery of a patient who had died of an unrelated cerebral tumor. The other, which was the cause of intestinal obstruction, had encircled only part of the circumference of the ileum but had spread to the adjacent mesentery and to the liver. Radical resection of the local lesion was performed. The patient died six years after recognition, and autopsy showed a small local recurrence and extensive liver involvement.

Lipoma

Lipomas of the small intestine are benign fatty tumors located in the submucosa and are usually pedunculated (Fig 3). Their importance clinically lies in the fact that they may initiate an intussusception. This occurred in 3 of our 9 cases. Two of these patients, who were successfully treated and are living and well, have been reported.^{1,2} The third patient had multiple submucous lipomas with intussusception, but the disease was not recognized ante mortem, although it was the cause of death.

Adenoma

Adenomas of the small bowel are small pedunculated tumors that may undergo malignant changes

ous stomach." Although it is obvious that the clinical picture may be obscure, patients with symptoms of chronic intermittent intestinal obstruction or of secondary anemia of gastrointestinal

X-RAY DIAGNOSIS

The accurate early diagnosis of tumors of the small intestine ultimately depends on careful roentgenologic barium-contrast studies. It is our

TABLE 2 *Symptoms in 30 Cases of Malignant Small-Bowel Tumor*

LESION	LOCATION	VOMITING	CONSTIPATION	ABDOMINAL PAIN	GROSS MELENA	SECONDARY ANEMIA	PALPABLE ABDOMINAL MASS
Adenocarcinoma (16 cases)	Duodenum	4	4	1	—	—	—
	Jejunum	5	5	—	—	2	1
	Ileum	4	4	—	—	1	1
Lymphosarcoma (13 cases)	Jejunum	1	1	1	—	—	1
	Ileum	6	6	10	5	—	10
Angiosarcoma (1 case)	Ileum	1	1	1	—	—	1

opinion must have roentgenologic investigation of the small intestine if an adequate explanation is not found in the stomach or colon.

Lymphosarcoma, in our experience, presented a more clear-cut picture, in that an abdominal mass

opinion that any patient with signs or symptoms referable to alimentary-tract obstruction or bleeding should have x-ray investigation of the small intestine, provided a satisfactory explanation for the clinical picture is not found in the esophagus,



FIGURE 3 *Submucous Lipoma of the Ileum*

The tumor was the leading point of an ileocolic intussusception. The diagnosis was made by barium enema.

was palpable in all except 2 patients. Abdominal pain of a crampy nature was also much more frequent, and there was usually no question that these patients had a serious abdominal disease. One patient had an ileocolic intussusception. In addition to the symptoms listed, all the patients with malignant tumors showed evidence of weight loss.

stomach or large intestine. In this respect it is well to remember that a peptic ulcer may coexist with a jejunal or ileal tumor.

Methods of Examination

Unless there is definite evidence of small-bowel obstruction, the course of the x-ray investigation

benign tumors can be the source of considerable blood loss,⁷ although there was no bleeding in our series. Intussusception, initiated by a benign tumor, is occasionally seen and is the usual way that such tumors cause intestinal obstruction. Intussusception was caused by benign lesions in 3 cases, all of

lymphosarcoma in that abdominal pain was rare and that 3 patients with carcinoma complained only of the symptoms of secondary anemia. Newton and Buckley³ pointed out that anatomically identical adenocarcinomas of the small bowel can present the picture of intestinal obstruction or can only show



FIGURE 2 Lymphosarcoma of the Ileum

As shown by the photograph of the gross specimen, this lesion is larger and more diffuse than that of the carcinoma shown in Figure 1. The tumor was easily palpable preoperatively. The extent of the lesion is more apparent in the photograph taken after the lumen had been opened.

which had submucous lipomas. Otherwise, the benign tumors caused no symptoms. Rankin and Newell⁷ reported 35 cases of benign tumors of the small bowel, in 18 of which the lesion caused hemorrhage or intestinal obstruction.

The symptoms caused by malignant lesions in 30 cases are summarized in Table 2. The duration varied from a week to two years, with an average of about four months for lymphosarcoma and five months for adenocarcinoma. The patient with malignant argentaffinoma had had symptoms for two years. Adenocarcinoma differed clinically from

symptoms of secondary anemia without any gastrointestinal symptoms, although the lesion may be high in the jejunum. It is of further interest that a palpable abdominal mass was observed in only 2 patients with carcinoma. Intussusception may be initiated by adenocarcinoma^{9,10} but was not present in our series. Another important point in the history of patients with small-bowel carcinoma is that many have had barium roentgenologic studies of the stomach and colon, not once but several times, with negative findings and have therefore occasionally been told that they have a "nerv-

Benign Tumors

Theoretically, benign tumors should be demonstrable by x-ray examination as polypoid or smooth, round filling defects in the lumen of the intestine. Such findings are not too infrequent in the duodenum, and illustrations are readily found in the radiologic literature¹⁵⁻¹⁷. On the other hand, it is exceedingly rare to demonstrate benign tumors *per se* in the jejunum or ileum. Golden¹¹ states that he

in the terminal ileum and causes intussusception of the ileum into the cecum, the lesion can be demonstrated by barium enema (Fig 4). If there is intussusception of one loop of small intestine into another, this may be demonstrated by oral barium. Since the filling is from the proximal side, the x-ray picture is that of a narrow, barium-filled tract lying within a loop of small intestine. If some of the barium passes distally, a thin layer may outline the intussusceptum lying within the lumen of the



FIGURE 4 Intussusception of the Ileum into the Cecum Caused by a Lipoma of the Ileum

The film on the left, taken before evacuation, shows the filling defect in the cecum made by the invaginated ileum. The film on the right, taken after evacuation, shows the calculeae cornuities of the terminal ileum as cross striations within the lumen of the cecum and lower ascending colon.

has never been able to demonstrate a benign neoplasm in this way. A review of the literature shows only one report of such findings, in which the authors describe 3 cases.¹⁸ This infrequency is probably due to segmentation and overlapping of intestinal loops obscuring the lesions because of their small size and to the fact that the tumors rarely give rise to symptoms leading to x-ray investigation until they have caused intussusception.

The demonstration of this associated intussusception is the most frequent x-ray finding in benign tumors of the small intestine. If the tumor occurs

in the terminal ileum and causes intussusception of the ileum into the cecum, the lesion can be demonstrated by barium enema (Fig 4). If there is intussusception of one loop of small intestine into another, this may be demonstrated by oral barium. Since the filling is from the proximal side, the x-ray picture is that of a narrow, barium-filled tract lying within a loop of small intestine. If some of the barium passes distally, a thin layer may outline the intussusceptum lying within the lumen of the

Malignant Tumors

Carcinoma The x-ray findings in carcinoma of the small intestine vary with the type of tumor growth. The usual finding is an annular constriction with concave, shelf-like margins. Roentgenology frequently demonstrates only the proximal margin with a narrow rigid tract of barium, representing the constricted lumen through the tumor, extending from it. Occasionally, both the proximal

should first rule out lesions in the colon, stomach and duodenum by the usual methods of x-ray examination — that is, the barium enema and gastrointestinal series. These examinations not only serve to exclude lesions in the colon, stomach and duodenum but also may give the first clue of the presence of a neoplasm in the jejunum or ileum. For example, the barium enema may disclose the presence of intussusception of the ileum into the colon on the basis of a tumor of the terminal ileum. This point is discussed in more detail below.

X-ray examination may also disclose segments of small intestine filled with air, fluid or barium that, in view of the symptoms, should immediately arouse suspicion of a tumor and lead to further investigation. At this hospital, the routine gastrointestinal series includes the giving of a barium motor meal six hours before the fluoroscopic examination. If, at the time of fluoroscopy, the barium meal demonstrates a dilated segment of jejunum or ileum or shows almost complete retention of the barium in the stomach, with no demonstrable point of obstruction proximal to the ligament of Treitz, obstruction beyond this point should be sought.

Occasionally, unrelated x-ray examinations give the first indication of a small-bowel lesion. In 1 case cholecystograms revealed several dilated, fluid-filled loops of small intestine faintly outlined by unabsorbed Priodax retained in the loops. Follow-up barium studies disclosed a jejunal tumor. The valuable role of plain films of the abdomen in disclosing distended air-filled intestinal loops indicating ileus or obstruction is well known and needs no further mention.^{11, 12}

If, in the presence of intestinal symptoms, the gastrointestinal series and barium enema disclose no disease, more intensive study of the small intestine by special technics is indicated. In general, there are three methods available to the roentgenologist.

Motility series. This procedure is employed at various clinics under different designations and with minor variations in details of technic. The method used at this hospital is as follows. Thirty grams of barium sulfate in water is given at 8 o'clock on the morning of the examination, all food and fluids having been withheld from the patient since the previous evening. Half an hour after the ingestion of the barium, a film is taken, and this is repeated at intervals of half an hour to an hour. Each film is inspected by the roentgenologist immediately after processing, and if any abnormal segments of intestine are seen, the patient is fluoroscoped and spot films are taken as indicated. The examination is completed after the head of the barium column has reached the cecum and the terminal ileum has been well visualized. In this way the progress of the

barium through the entire jejunum and ileum can be followed.

Small-bowel enema. An alternative method of examination is the small-bowel enema, as described by Schatzki.¹³ This procedure consists of the passage of a Levine or Miller-Abbott tube into the duodenum so that its tip lies in the second portion. Under fluoroscopic observation, the entire small intestine is filled with a barium suspension that is allowed to run in through the tube in a slow uninterrupted flow. Spot films are taken during the examination as indicated.

The two methods outlined above may be used even in the presence of a partially obstructing lesion without danger of completing the obstruction, since the fluid state of the barium suspension is preserved in the ileum and jejunum and since there is no dehydrating action. Golden¹⁴ states that no evidence of damage was observed after the administration of barium by mouth in the presence of disease of the small intestine, even with narrow constrictions. One of our patients offered excellent proof of this opinion. The operative specimen showed a markedly constricting carcinoma of the jejunum through which air could be forced only with difficulty, and yet a few days prior to operation, barium administered by mouth passed readily through this area to the cecum with only slight delay proximal to it and with no evidence of a deleterious effect or barium plug at operation.

If complete intestinal obstruction with ileus is present, the two methods described above should not be used because the amount of barium suspension necessary for the examination further distends already dilated loops and is difficult to withdraw through a tube with a narrow lumen. Furthermore the procedures do not yield satisfactory results because the overlapping dilated barium-filled loops of intestine obscure the lesion, the barium is diluted greatly in the obstructed loops, and motility is absent or diminished, causing stasis of the barium proximal to the lesion. If it is desired to demonstrate the cause of an obstruction, the following method may be used.

Modified small-bowel enema. A Miller-Abbott tube is passed into the intestine, usually as a therapeutic measure when the patient is first seen. After the tube has reached the point of maximum progress and the dilated loops have been decompressed by suction, a small amount of thin barium suspension (35 to 40 cc) is introduced through the tube just proximal to the obstruction and under fluoroscopic observation the area of obstruction is examined.¹⁴ In this way much valuable information may be gained, and frequently the exact nature of the lesion demonstrated.

highly suggestive sign of these tumors. Recently, we saw in consultation the x-ray studies of a patient who was found to have an argentaffinoma involving the terminal ileum. The films showed a fairly smooth narrow segment of intestine about 10 cm in length and with the diameter of an ordinary lead pencil. It was concave, as if stretched around a soft-tissue mass. The mucosa through the segment appeared intact but was distorted, having a fine granu-

Swenson²² described a generalized lymphosarcomatous involvement of the small intestine in which x-ray examination showed a patchy irregular distribution of barium through the jejunum and upper ileum, with coarse irregular wall markings widely separated. Hypomotility was present. The picture resembled that seen in nutritional disturbances, such as sprue. Tannhauser and Davison²³ also described a case of the generalized form of

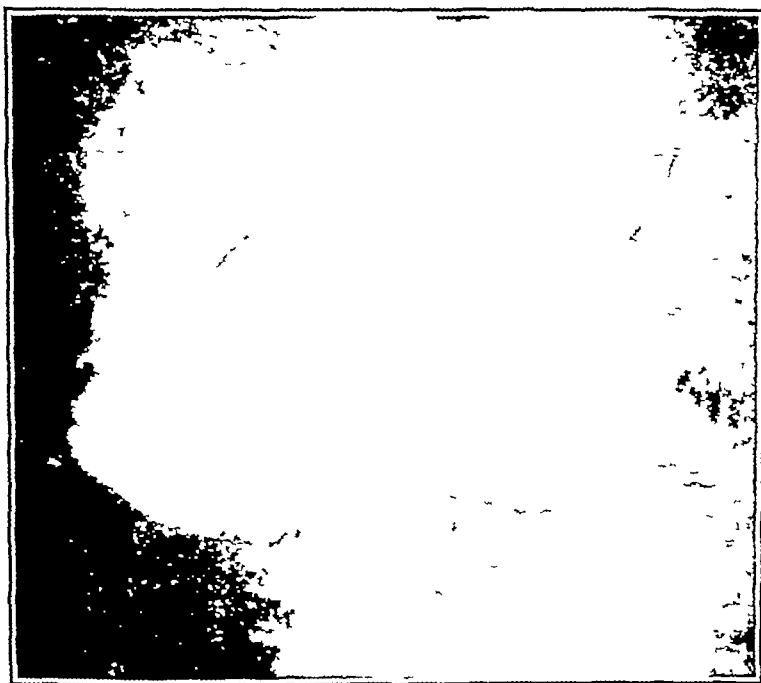


FIGURE 6 Carcinoma of the Jejunum

This tumor had produced intestinal obstruction. All the barium lies in the dilated intestinal loops proximal to the lesion, which is not outlined. The roentgenogram illustrates the "closed accordion" appearance of the dilated proximal loops, with the valvulae conniventes lying closely together.

lar appearance. There were no shelflike margins at the ends of the lesion. Fluoroscopically, it was reported to be fixed and rigid. The appearance was similar to that seen with long-standing chronic cicatrizing enteritis, or with involvement of a segment of intestine in an extrinsic chronic abscess of the peritoneal cavity.

Small benign nodular submucosal carcinoids should show, theoretically, smooth dome-shaped or polypoid filling defects projecting into the lumen, frequently multiple. No reports of the demonstration of such lesions could be found in the literature or in our own records. A carcinoid as the basis of an intussusception of the ileum into the cecum was reported by Brocher.²¹

Sarcoma. Lymphosarcoma is the most frequent sarcoma involving the small intestine. This involvement may be either localized or generalized

gastrointestinal pseudoleukemia in which there were numerous polypoid growths throughout the intestine showing as multiple small intraluminal filling defects on x-ray study. The localized form may present an x-ray appearance identical with that of carcinoma. As Doub and Jones²⁴ state, the tumors may be divided into three groups: the annular constricting lesions, which they consider rare in sarcoma; the subserous tumors, which show ulcerated and aneurysmal dilatations of the lumen of the involved segment; and those that present a polypoid intraluminal mass. In general it may be said that lymphosarcoma tends to involve a longer segment of intestine than carcinoma and less often causes marked constriction. The involved segment shows either an irregular lumen of normal or slightly less than normal caliber or actual dilatation and widening of the lumen owing to ulceration and necrosis.

and the distal concave margins with a constricted area between them may be shown, giving the typical napkin-ring appearance seen in annular carcinomas of the colon (Fig 5). The involved area is usually short, being less than 5 cm in length, rigid and often fixed. The mucosal pattern through it is destroyed. The lesion is more circumscribed in carcinoma than

ulceration within the tumor. The involved area is much longer than that seen with the annular type, all the reported lesions measuring several centimeters in length and the longest measuring 14 cm.

Frequently, the roentgenologist is able to demonstrate only the point of obstruction with dilated loops proximal to it, his interpretation must then be



FIGURE 5 Adenocarcinoma of the Jejunum

The roentgenogram on the left, an area of the plain film made during fluoroscopy, shows the constricting lesion with the characteristic biconcave shelf formation at either end. The roentgenogram on the right is of the specimen removed at operation which was clamped at both ends and filled with air. It is apparent that the annular constricting lesion almost completely obliterated the lumen. This is the case illustrated in Figure 1.

in lymphosarcoma. Proximal to the lesion the intestine is frequently dilated and may show accordion-like pleating of the valvulae conniventes of the portion just adjacent to the tumor (Fig 6). This is the probable result of contractile shortening of the longitudinal muscles of the intestinal wall in an attempt to overcome the obstruction. Intraluminal proliferative polypoid carcinomas are rarer and show on x-ray examination an irregular filling defect projecting into the lumen. Golden¹¹ reports an infiltrating type of carcinoma of the terminal ileum much longer than that ordinarily seen, with irregular borders resembling an inflammatory type of lesion. The x-ray appearance of a group of carcinomas classified as nonobstructing and extraluminal has been described by Lingley.¹² These give the x-ray picture of a large, dilated, irregular, barium-filled segment of intestine associated with a palpable mass. This appearance is the result of extensive necrosis and

limited to an obstructing lesion of the small intestine of undetermined nature. Malignant, as well as benign, tumors may give rise to intussusception, with x-ray findings similar to those described above under benign tumors.

Argentaffinoma. The malignant variety of this lesion may cause an annular constriction, with an x-ray appearance that is indistinguishable from an annular carcinoma. Miller and Herrmann²⁰ point out that the intraluminal portion of a carcinoid that has undergone malignant change is frequently not large but that there is extension into the wall of the intestine and into the mesentery, with resultant kinking or knuckling of the intestine at the site of the tumor that produces obstruction, either partial or complete. They demonstrated these x-ray findings in 3 proved cases of carcinoid and concluded that the roentgenologic demonstration of a tumor at a point of kinking and partial obstruction is a

diagnosis The lesions may likewise be the basis of intussusception This is especially true of myosarcomas

TREATMENT

The treatment of choice is resection of the involved segment of bowel along with its adjacent mesentery and restoration of the continuity of the intestine In the jejunum and ileum, resection and end-to-end or side-to-side anastomosis is performed The duodenum, however, presents a more complicated technical problem because of its anatomic

and well four years after resection of the ileum for lymphosarcoma, when he was lost to follow-up One patient* is living and well six years after resection of a carcinoma of the jejunum A single patient with a recent case of carcinoma of the jejunum is living and well seven months postoperatively The obvious causes for these poor therapeutic results are the facts that the diagnosis is made late and that the tumors metastasize early via the lymphatic vessels

The 2 cases of intussusception caused by submucous lipomas of the small intestine were treated by resection and end-to-end anastomosis Both

TABLE 3 *Surgical Procedures in 32 Cases of Small-Bowel Tumor*

Lesion	Site	RESECTION AND ANASTOMOSIS	SIDETRACKING ENTERO-ENTEROSTOMY	EXPLORATORY LAPAROTOMY AND BIOPSY	POSTERIOR GASTRO-ENTEROSTOMY	CHOLECYSTO-GASTROSTOMY	ENTEROSTOMY	SUBTOTAL GASTRIC RESECTION (POLY)	NO SURGERY
Adenocarcinoma	Duodenum	5		2	1	1		2	2
	Jejunum	3	2						
	Ileum		1						
Lymphosarcoma	Jejunum	5	1	3		1			2
	Ileum								
Argentaffinoma	Ileum	1							
Totals		14	4	5	1	1	1	2	4

position None of the lesions of the duodenum in our series were operable, but the logical attack on a malignant primary tumor of the duodenum is along the lines pointed out by Whipple²⁶ for resection of carcinoma of the head of the pancreas or the ampulla of Vater An excellent review of the types of operative procedures in this field is given by Orr.²⁷ X-ray therapy was given postoperatively to all patients with lymphosarcoma The radiosensitivity of these tumors is well known,^{28, 29} but the results are usually temporary and palliative

A summary of the surgical procedures in this series is given in Table 3 In only 2 patients with adenocarcinoma of the duodenum was the diagnosis apparent at the time of operation, and both lesions were inoperable In the other 2 cases in this group carcinoma was found incidentally on microscopical examination of the specimen removed at subtotal gastrectomy for duodenal ulcer One of these patients is living and well ten years after operation, and the other did not respond to follow-up query The malignant tumors of the jejunum and ileum were resectable in 14 of 24 cases, and in the remainder, an exploratory operation, alone or in combination with a palliative sidetracking procedure, was done Four patients had no operation

The survival period for the patients with malignant tumors of the jejunum and ileum was universally short The average survival of 22 patients who underwent operative procedures was eleven and a half months for adenocarcinoma and six months for lymphosarcoma There was no response to follow-up query in 3 cases, but 1 patient was living

and well five and fifteen years respectively after operation Excellent results should be achieved in benign lesions, provided that the complicating obstruction or hemorrhage is recognized before it becomes irreversible It should be remembered that benign lesions may be multiple, and the whole small bowel should be explored if the patient's condition warrants it

SUMMARY

Sixty-five cases of benign and malignant primary tumors of the duodenum, jejunum and ileum are reviewed In 33 the tumors were malignant 18 were adenocarcinomas, 13 were lymphosarcomas and 2 were invasive argentaffinomas

Thirty-three patients had symptoms caused by small-bowel tumors of which 30 were malignant tumors Only 3 benign tumors were the cause of symptoms, and in each case there was an associated intussusception

The ileum was the most frequent portion of the intestine involved, but 13 cases of adenocarcinoma occurred in the duodenum or jejunum

The symptoms of small-bowel tumor are those of obstruction or anemia following bleeding into the alimentary tract No characteristic clinical picture was presented

The diagnosis depends on thorough barium-contrast roentgenologic investigation of the small bowel in every patient with suggestive symptoms

*This is a patient of Dr. Robert Zollinger who studied her in this hospital but performed the operation at an outside hospital The case represents one of the longest survivals of carcinoma of the small intestine that we have been able to find

Lymphosarcoma is likelier to produce multiple lesions than carcinoma, and there is frequently an associated palpable mass. The involved area is usually more irregular than that of carcinoma.

Swenson²² states that x-ray examination frequently shows a longer segment to be involved than

on nonobstructing extraluminal malignant tumors. Lingley¹⁹ described 3 cases in which the sarcoma presented an x-ray appearance similar to that discussed above under carcinoma. This appearance is more frequently seen with sarcoma than with carcinoma. Sarcomas, like the other malignant tumors,



FIGURE 7 *Lymphosarcoma of the Terminal Ileum*

This roentgenogram shows irregularity of the involved ileum, with filling defects distal to the ileocecal valve, which indicate involvement of the cecum. The mucosa is destroyed throughout the area of the lesion. The caliber of the involved bowel is normal or only slightly constricted. Lymphosarcoma produces changes closely resembling inflammatory lesions.

is actually found at operation or autopsy. He believes that this is caused by mesenteric extension of the tumor, with blocking of the lymphatic vessels and disturbance of the autonomic nervous control causing distortion of the mucosa and the lumen beyond the actual limits of the tumor. In an article

may produce lesions that remarkably resemble cicatrizing enteritis on x-ray study, especially if they occur in the terminal ileum. Menne²⁵ reported such a case, and one of our cases presented this appearance (Fig 7). Associated involvement of the cecum seen with sarcomas may help in the differential

of the first four lumbar vertebrae. The tissues down to the transverse processes were then infiltrated with 1 per cent procaine, a 22-gauge, 7.5-cm needle being used. Particular attention was given to the muscle fascia and the periosteum of the transverse processes, because contact with these structures was invariably uncomfortable. Next, 20-gauge, 12.5-cm sympathetic-block needles were inserted through wheals perpendicular to the skin to make contact with the transverse processes. The needles were then withdrawn and redirected about 30° medialward and 30° cephalad, so as to pass above the transverse processes until the body of

swung into the frontal plane of the body and perpendicular to the midline. In this position, the needle lay almost flush with the skin of the supraclavicular area. On further introduction the tip impinged on bone either of the transverse process of the seventh cervical vertebra or the neck of the first rib or the body of the seventh cervical vertebra between these two points. Approximately 8 cc of 2 per cent procaine solution was then injected.

OBSERVATIONS

All patients treated showed definite improvement of the peripheral vascular system. Changes usually

TABLE 1 *Results of Sympathetic Block or Polioin diets*

Case No.	SYMPTOMS	ONSET OF DISEASE	DURATION	NO OF BLOCKS	OSCILLOMETRIC MEASUREMENT		RESULT
					BEFORE BLOCK	AFTER BLOCK	
1 37	Marked spasm and tenderness of gastrocnemius muscle with throbbing pain	December 1945 (Philippine Islands)	4	4	2.5-3	6-7	Relief of spasm tenderness and pain
2 19	Hyperhidrosis of hands spasm and tenderness of right arm	April 1946 (Philippine Islands)	2	2	—	—	Relief of spasm and tenderness hands dry
3 32	Severe pain and tenderness	July 1946 (Mississippi)	—	2	5-6	6-7	Relief of spasm tenderness and pain, feet warm and dry
4 39	Bilateral cyanosis, sweating and coldness chilblains and edema	September 1945	5	6	2-3	7-7.5	Relief of paresthesias and improvement of edema feet warm pink and dry with occasional cyanosis on dependency
5 31	Marked coldness and bilateral hyperhidrosis	December 1945 (India)	7	2	1-1.5	4-4.5	Feet warm and dry
6 24	Marked cyanosis coldness and sweating with paresthesias and some pain	March 1945 (Tunis)	10	—	2	5.5-7	Relief of paresthesias feet warm dry and pink
7 23	Marked cyanosis coldness and sweating	August 1945	6	—	1-1.5	3-4	Feet warm and dry
8 26	Marked cyanosis moderate coldness and sweating	August 1940 (New York)	60	3	4-	6-7.5	Feet warm and pink
9 22	Marked coldness and sweating with moderate cyanosis of both feet	August, 1945 (France)	6	—	3.5-4	6-7	Feet warm and dry
10 —	Marked coldness and cyanosis moderate sweating some paresthesias	June 1945 (Italy)	7	4	—	—	Relief of paresthesias feet warm and dry
11 39	Moderate coldness and sweating with some cyanosis mild paresthesias	April 1945 (Philippine Islands)	9	2	—	—	Relief of paresthesias feet warm and dry
12 21	Paresthesias of legs	August, 1945 (New Jersey)	7	3	—	—	Relief of paresthesias
13 24	Moderate edema, cyanosis and coldness	July 1945 (Texas)	7	2	—	—	Progressively diminishing edema to normal in four weeks
14 27	Marked cyanosis and coldness moderate sweating and edema	September, 1945	6	3	1-2.5	4-5	Feet warm dry and pink progressively diminishing edema for three weeks
15 27	Marked sweating and paresthesias moderate cyanosis and coldness	June 1945	8	2	—	—	Relief of paresthesias after four months feet warm and dry
16 33	Hyperhidrosis marked coldness and moderate cyanosis	June 1945 (England)	8	2	1	5-6	Feet warm and dry
17 21	Marked edema cyanosis, coldness and sweating of feet	April 1945 (United States)	—	3	1-1.5	5-6	Improvement of edema feet warm and dry

the vertebra was touched. As soon as contact with the body had been made, the needle was further introduced so as to slide off the body of the vertebra and to be near the anterolateral surface of the body. After aspiration showed the needle not to be in a blood vessel, 6 cc of 2 per cent procaine was injected.

Stellate-ganglion block was performed by an anterolateral approach, similar to that of Volpitta.³ The midpoint of the clavicle on the side to be injected was located, and a skin wheal raised about 2 cm above this point. A 22-gauge, 7.5-cm needle was inserted through the skin wheal downward medially and posteriorly to make contact with the first rib. The needle was then withdrawn and

occurred within five or ten minutes after injection. Subjectively, many patients experienced a "hot foot," and stated, "I can't remember when my foot felt so good." The duration of this improved feeling following the first block was about three days. After subsequent blocks the improvement was progressively prolonged. In 8 cases after the third block there was subjective improvement for ten weeks. In Case 4 after the third block improvement lasted for four months (Table 1).

Objectively, all manifestations of vasospasm disappeared within twenty minutes after procaine injection. Color changes occurred early and were closely followed by a rise in temperature, the transition from a cold cyanotic extremity to a warm pink

unless a satisfactory cause is found in the stomach or colon

The indications and methods of roentgenologic investigation are described in detail

The treatment of choice is radical surgery, but the results of such therapy in malignant small-bowel tumors are poor

Earlier diagnosis is the only way in which the results of treatment can be improved, and that depends on the more frequent examination by barium-contrast roentgenologic studies of the small bowel

REFERENCES

- Oughterson A W, and Cheever D Recurring intussusception caused by intestinal neoplasms, requiring multiple operations for its relief *Surg, Gynec & Obst* 48 682-686 1929
- Botsford T W and Newton, F C Intussusception in adult due to submucous lipoma of ileum *Surgery* 10 265 269 1941
- Newton, F C and Buckley, R C Primary adenocarcinoma of jejunum with report of two cases *New Eng J Med* 202 255 261, 1930
- Bailey, O T Argentaffinomas of gastro-intestinal tract, benign and malignant *Arch Path* 18 843 864 1934
- Shallow T A, Eger, S A, and Cartz J B Primary malignant disease of small intestine *Am J Surg* 69 372 383 1945
- Horsley, J S Carcinoma of jejunum and of ileum *J A M A* 117 2119 2123, 1941
- Rankin, F W, and Newell C E Benign tumors of small intestine report of twenty four cases *Surg Gynec & Obst* 57 501 507 1933
- Ratford T S Tumors of small intestine their diagnosis with special reference to x ray appearance *Radiology* 16 253 270 1931
- Rankin, F W, and Mayo, C Jr Carcinoma of small bowel *Surg Gynec & Obst* 50 939 947 1930
- Rose, B T Carcinoma of small intestine *Brit J Surg* 33 186 1945
- Golden, R *Radiologic Examination of the Small Intestine* 239 pp Philadelphia J B Lippincott Co 1945
- Holmes, G W, and Ruggles H E *Roentgen Interpretation Sixth edition* 364 pp Philadelphia Lea & Febiger, 1941
- Schatzki, R Small intestinal enema *Am J Roentgenol* 50:741-751, 1943
- Blodgett, J B Technique for satisfactory use of Miller-Abbott tube. *Am J Surg* 53 271-279, 1941
- Golden R Non malignant tumors of duodenum *Am J Roentgenol* 20 405-413, 1928
- Carman, R D Hemangioma of duodenum *Am J Roentgenol* 8 481, 1921
- Templeton, F E *X-ray Examination of the Stomach A description of the roentgenologic anatomy, physiology, and pathology of the esophagus, stomach, and duodenum* 516 pp Chicago University of Chicago Press 1944
- Talia, F, and Ficari, P Sui tumori polipoidi del duodeno e del tenue (studio clinico-radiologico-operativo) *Arch. di rasist.* 12 190-220, 1936
- Lingley, J R Non-obstructing malignant tumors of small bowel. report of five cases *Am J Roentgenol* 36:901-909, 1936
- Miller, E R, and Herrmann, W W Argentaffin tumors of small bowel roentgen sign of malignant change *Radiology* 39 114-120, 1942
- Brocher J E W Invagination iliocecale à la suite d'un carcinome. *Rev méd de la Suisse Rom* 48 50-53 1928
- Swenson, P C X ray diagnosis of primary malignant tumor of small intestine *Rev Gastroenterol* 10 77 91, 1943
- Tannhauser, S and Davison, R Gastro-intestinal pseudoleukemia (report of case) *Am J Digest Dis* 7 45-49, 1940
- Doub H P and Jones H C Roentgenologic diagnosis of tumors of small bowel *Am J Digest Dis* 8 149 154 1941
- Menne F R, Mason, D G and Johnston, R. Lymphosarcoma of intestine report of two cases *Arch Surg* 45 945 956 1942
- Whipple A O Surgical treatment of carcinoma of ampullary region and head of pancreas *Am J Surg* 40 260-263, 1938
- Orr T G Pancreatoduodenectomy for carcinoma of ampulla and ampullary region *Surgery* 18 144-158 1945
- Chont L K Sarcomas of small intestine and reference to their radio-sensitivity *Radiology* 36 86-97, 1941
- Cutler, M Buschke, F and Cantrell S T *Cancer - Its Diagnosis and Treatment* 757 pp Philadelphia W B Saunders Co., 1939

VASOMOTOR DISTURBANCES IN POLIOMYELITIS, WITH SPECIAL REFERENCE TO TREATMENT WITH PARAVERTEBRAL SYMPATHETIC BLOCK

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POLIOMYELITIS in adults can no longer be considered unusual Lewin¹ states that the incidence is definitely increasing in the older age groups At the Army and Navy General Hospital, Hot Springs, Arkansas, a center for poliomyelitis patients, 131 cases in military personnel were studied Practically all the cases were convalescent—that is, the acute symptoms had subsided and the patients were observed prior to the end of the two-year interval arbitrarily set as the convalescent period

In a review of these cases vasomotor and sudomotor disturbances frequently appeared in the extremities These changes formed an important part of the symptomatology and consisted of varying degrees of cyanosis or discoloration of the skin, accompanied by mild to severe edema and hyperhidrosis The most frequent indications of vasomotor disturbances were coldness and sweating of the part involved

In an attempt to alleviate these distressing symptoms complicating poliomyelitis, paravertebral sympathetic blocks were performed, the results in 17 cases are reported below

TECHNIC

Patients scheduled for sympathetic block were premedicated with 0.2 gm of sodium amytal ninety minutes prior to nerve block and with a small dose of morphine and scopolamine one hour prior to nerve block Lumbar paravertebral sympathetic block was performed on patients with involvement of the lower extremities, and stellate-ganglion block on those with involvement of the upper extremities

The technic of lumbar sympathetic block employed was essentially that of Ochsner and DeBakey.² Patients were placed in the lateral recumbent position, for purposes of comparison, only one side was given a course of injections at a time The landmarks employed were the spinous processes, the transverse processes and the bodies of the lumbar vertebrae Skin wheals were raised 4 to 6 cm lateral to the upper part of the spinous processes

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that 21 of 158 cases in New York had varying degrees of muscle spasm eight months after the acute illness. These workers also stated that they had no specific remedy for muscle spasm. In view of the results in 3 of our cases it seems probable that impulses producing pain and spasm are mediated in part by the sympathetic system and that relief can be obtained by sympathetic nerve blocks. It is also suggested that sympathetic blocks may relieve the pain, spasm and muscle tenderness in the acute phase of poliomyelitis as dramatically as it did in our 2 cases in the convalescent stage and 1 case in the acute stage. Therefore, with this report as a background, it is hoped that further investigations will be carried out to determine the status of sympathetic blocks and their efficacy in poliomyelitis.

SUMMARY

Vasomotor disturbances, such as edema, hyperhidrosis, coldness and chilblains, are frequently encountered in the convalescent period of poliomyelitis.

Sympathetic nerve blocks were employed to alleviate these distressing manifestations of disturbed vasomotor activity with partial to complete relief in 15 cases.

Pain, muscle spasm and muscle tenderness were completely relieved in 3 cases by sympathetic nerve blocks and without supplementary therapeutic measures, such as physiotherapy and hot packs.

It is suggested that the pain, tenderness and muscle spasm in the acute phase of poliomyelitis may also be alleviated by sympathetic blocks.

REFERENCES

1. Lewin P. *Infantile Paralysis: Anterior poliomyelitis*. 372 pp. Philadelphia: W. B. Saunders Co. 1941.
2. Ochsner A and DeBakey M. Therapeutic considerations of thrombophlebitis and phlebotrombosis. *Ann Eng J Med* 225:207-227, 1941.
3. Volpittio P P and Risteen W A. Stellate ganglion block: definite anterolateral approach. *Anesthesiology* 5:491-494, 1944.
4. Harris R J and McDonald J L. Effect of lumbar sympathectomy upon growth of legs paralyzed by anterior poliomyelitis. *J Bone & Joint Surg* 18:35-43, 1936.
5. Onizkie W H. Place of operations upon sympathetic system in treatment of poliomyelitis. *Proc Ro Soc Med* 26:429-436, 1933.
6. Robertson D E. Sympathectomy in children. *Surg Gynec & Obst* 58:312-317, 1934.
7. Hanson K G and Straub L R. Report on poliomyelitis cases from Hospital for Special Surgery of New York City. *New York State J Med* 46:1003-1014, 1946.

AN ERUPTIVE FEVER INVOLVING THE SKIN AND MUCOUS MEMBRANES (STEVENS-JOHNSON DISEASE)*

ARNALL PATZ, M D

BALTIMORE

IN 1866 von Hebra¹ first described erythema multiforme as a generalized skin eruption without marked systemic symptoms, a rare type with fever, malaise, prostration and an accompanying severe stomatitis and purulent conjunctivitis was mentioned. Kaposi,² in 1893, described an infrequent form with involvement of the mucous membranes. More recently, reports of erythema multiforme with occasional involvement of the mucous membranes of the eyes, mouth and genitalia have been presented.³⁻⁵

In 1922 Stevens and Johnson⁶ reported 2 cases of "a new eruptive fever associated with stomatitis and ophthalmia." They believed that the features of their cases, although previously described as a rare form of erythema multiforme, justified consideration as a separate entity. Many strikingly similar cases have subsequently been reported. The almost identical clinical pictures certainly merit recognition as a distinct syndrome. The name "Stevens-Johnson disease" has been used by many writers for this clinical entity.

The disease is usually characterized at the onset by mild conjunctivitis and stomatitis, which are followed in one or two days by fever, prostration

and a generalized erythematous skin rash that undergoes hemorrhagic or vesicular changes. By the end of the first week, the stomatitis becomes ulcerative or bullous, and the conjunctivitis severe, with a copious purulent discharge. Corneal ulceration with opacification or subsequent endophthalmitis is not infrequent. The usual period until resolution of the mucous-membrane lesions is two weeks. The skin lesions resolve in about three weeks. No known etiology of the disease has been established. Two fatal cases have been reported.

The following case is considered typical.

An 8-year-old boy of Italian descent was admitted to the hospital on May 15, 1945. Five days before admission an upper respiratory infection with burning, watery eyes and a sore throat had developed. On the following day the mouth became exquisitely tender and the upper lip swollen, with several small blisters; simultaneously, a discrete, purplish macular dime-sized lesion on the left forearm and an identical one on the abdomen were noted. Three days before admission the eyes became acutely inflamed and swollen. A physician found the temperature to be 102°F, and the patient was started on sulfadiazine. On the following day burning on urination and soreness about the glans penis were noted. Sulfadiazine was continued during the 3 days prior to admission. The temperature remained elevated between 101 and 102°F. The stomatitis, conjunctivitis, and balanitis became more intense, and on admission, the violaceous rash had become generalized. There was no history of the administration of other medications, including the sulfonamides. The past history revealed the usual childhood diseases.

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one was rapid and intense. Diminution in sweating occurred slowly, but a dry extremity was usually found within twenty minutes.

Edema cleared up slowly in all cases. Three patients remarked that on the day following their first sympathetic block they could get into a slipper easily. Generally, however, swelling diminished after the second block and continued thereafter. In Case 4 circumferential measurements of the left ankle showed a change from 33.6 cm. before the first block to 28.5 cm. eighteen days later. The right ankle diminished in size from 31.7 cm. to 27.3 cm. over a period of thirty days.

Oscillometric recordings were made at the ankle of many patients. Readings made prior to injection gave an average excursion of 1.5, with a range from 0.5 to 2.5. Post-block recordings in all patients were increased. The excursions varied from 4.0 to 9.0 with an average reading of 5.0. Thus, there was an average increase of 3.5 over the preblock measurements.

Of unusual significance were the observations on 3 patients with spasm, tenderness and pain, and these cases are therefore presented in detail.

CASE 1 A 25-year-old Army nurse contracted poliomyelitis in the Philippine Islands in February, 1946, with paresis of the hamstring, gastrocnemius and soleus muscles bilaterally. She was transferred to the Army and Navy General Hospital in April, 1946. Her chief complaint on arrival was not the paresis but the severe pain, tenderness and muscle spasm involving the hamstring, gastrocnemius and soleus muscles. Because of the slight edema, dusky coloration and coldness of the feet paravertebral sympathetic lumbar blocks were performed. Following the first block on May 29 there was temporary relief of the vasospastic phenomena on the more affected side, but there was complete relief of the pain and muscle spasm lasting for 20 days, whereas on the unblocked side the symptoms were still marked. Subsequent blocks of both right and left sympathetic ganglions resulted in complete relief. This relief persisted, and the patient was sent home on convalescent leave on July 25.

CASE 2 A 20-year-old soldier contracted anterior poliomyelitis on April 16, 1946, while on shipboard returning to the United States from the Philippines. The chief manifestations were in the shoulder girdle, with particular involvement of the deltoid and triceps muscles. Later, weakness of the lower muscle groups, especially the quadriceps, developed. The patient was at first treated with hot packs and passive exercises. He was transferred to the Army and Navy General Hospital on May 30.

On June 4 tenderness and spasm were present in the biceps and triceps muscles of the right side. Stellate-ganglion block performed on the right resulted in an intense Horner's syndrome, the right arm and hand became dry and hot. Subsequent to the block the patient was amazed at the new and improved feeling in the right arm. He stated, "My right arm is now better than my left." Objectively, there was absence of tenderness and no detectable spasm. A second block was performed 2 days later, and the improved state had continued at this writing.

CASE 3 A 32-year-old staff sergeant contracted poliomyelitis on July 9, 1946, in Louisiana. He was transferred to the hospital on July 25. Physical examination revealed bilateral lower-extremity paresis, complete on the right and partial on the left. The chief complaint at that time was extreme pain, tenderness and muscle spasm that kept the patient awake at night. The right lumbar sympathetic ganglions were blocked on July 29, and there was subsequently little tenderness or pain. For the first time since the onset of the illness the patient had a good night's sleep and did not require analgesics. A second block 2 days later re-

sulted in further improvement. Hot packs had been used initially, but only the expected mild comfort was obtained, whereas following the blocks improvement was sharp and definite.

DISCUSSION

The cause of vasomotor disturbances in poliomyelitis has not been completely explained. The intensity of such disturbances is variable, and although a patient may have extensive paralysis, the vasomotor changes do not necessarily parallel the paralysis. Neuropathologically, there is involvement of the intermediolateral cell columns whence the efferent preganglionic fibers arise to pass by way of white rami communicantes to the sympathetic trunk and ganglions. The postganglionic fibers passing via the gray rami are distributed to the vascular system. By alteration in the blood supply to a region the trophic state of the tissues and their metabolism can be influenced. In view of this, Harris⁴ performed sympathectomy with the purpose of promoting the blood supply thereby accelerating bone growth. He noted that sympathectomy resulted in a warm, dry, pink extremity and also that bone growth was apparently enhanced.

In 1933 Ogilvie⁵ reported on sympathectomy for the treatment of vasomotor and sudomotor disturbances in poliomyelitis. In 4 cases lumbar sympathectomy resulted in warm, dry and pink extremities, but this state was only temporary.

In 1934 Robertson⁶ reported on the use of sympathectomy in 68 children with poliomyelitis in the chronic stage. The immediate results were good in the majority of cases, and although a long follow-up period was not possible in every case, several patients had warm, dry and pink extremities at the end of five years.

In the present series of cases with treatment by chemical sympathectomy the results were encouraging (Table 1). Several patients followed for six months after the course of blocks demonstrated continued relief. It is believed that if there is a severe recurrence of vasomotor disturbance, further blocks will be beneficial, and the patients have been so advised. Because of these encouraging results in adults, the question of sympathetic nerve block in children arises. From the standpoint of the anesthesiologist complete co-operation on the part of the patient is needed for successful regional block procedures. This is difficult to obtain in children, but the results in adults are considered to warrant a trial in children, and it is recommended that the cases be selected carefully and attention paid to good premedication.

The problem of treatment of muscle spasm also deserves further investigation. Most textbooks state that muscle spasm subsides in four to eight weeks, but experience with over 130 adult patients with poliomyelitis indicates that spasm and muscle tenderness may persist for several months, and these cases are not exceptional. Hansson and Straub⁷ reported

these cases, however, lacked ocular involvement. The authors suggested that Vincent's infection, associated with altered tissue sensitivity, is an etiologic factor in Stevens-Johnson disease. Oral smears in typical cases, however, have not shown the organism of that infection.

The blood picture is not characteristic. The white-cell count is usually normal or slightly elevated. The case reported above is the first to show a persistent leukopenia. It is interesting to note that in over half the reported cases, the skin eruption is described as hemorrhagic or purpuric at some time during the illness. The purpuric char-

acter may necessitate parenteral feedings for several days. Involvement of the mucous membrane of the genitalia has been reported in approximately a fourth of the cases. The electrocardiographic changes are probably nonspecific and due to the prolonged febrile illness. Edgar and Syvertson¹⁵ reported auriculoventricular block, with changes in the ST segments, in a twelve-year-old patient.

Recurrences of the disease are not rare. In 1 of Edgar's cases, complete relapses occurred six months and eleven months after discharge.

There is no specific therapy for the condition. Penicillin administration to combat secondary in-

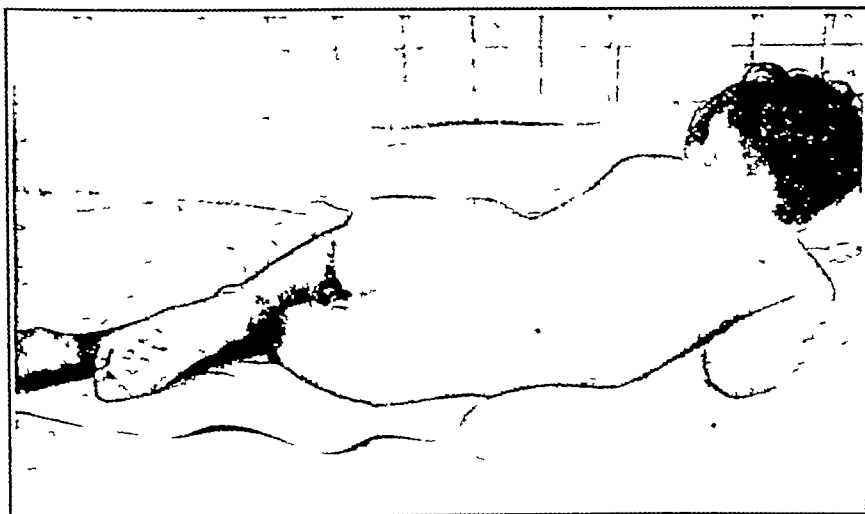


FIGURE 2 Photograph Showing the Generalized Eruption

acter of the lesions, which was prominent in the case presented above, is believed to have been associated with the thrombocytopenia. The possibility that low platelet counts existed in similar cases with purpuric tendencies should be considered, although no previous platelet studies have been reported. The patient in the case reported above received sulfadiazine during the seventy-two hours prior to admission, thrombopenia and leukopenia resulting from this medication are a remote possibility. The eosinophil count of 6 to 12 per cent is unexplained. In 3 other cases a moderate eosinophilia was reported.^{15 18 23}

Two fatal cases have been reported in which the syndrome was associated with severe respiratory infections.²⁴ Serious ocular sequelae have frequently been reported. Corneal ulceration with opacification may result, and perforation of the globe with enophthalmus and panophthalmus is not infrequent.¹¹ This has necessitated enucleation in several cases. The stomatitis is usually vesicular or ulcerative, and the membrane sloughs, leaving a raw buccal and palatal surface. The severity of the stomatitis

together with general supportive care, has given the best therapeutic results.

Several cumbersome names have been used to describe this entity, many cases being reported under the titles, "erythema multiforme bullosum with involvement of the mucous membranes," "mucosal respiratory syndrome" and "erythema multiforme plurionficialis." Some observers maintain that the mucosal involvement is simply a symptom of erythema multiforme and that the syndrome should not be considered a distinct entity. Weisberg and Rosen²⁷ have championed this view. Since it is the enanthem rather than the exanthem that seems to be striking, regarding the disease simply as a symptom of erythema multiforme does not stress the more important features. Regardless of the name used, the recognition of the syndrome in its own right is essential.

SUMMARY

A review of the classic cases of erythema multiforme with mucous-membrane involvement (Stevens-Johnson disease) is presented.

There was no history of allergy. The family history was noncontributory.

Physical examination disclosed a patient who appeared acutely ill and shielded the eyes from the light. The skin of both the upper and lower extremities and the trunk was covered with a maculopapular violaceous rash, each lesion had a discrete, rounded border and measured 5 to 20 mm in diameter. Many of the lesions were vesicular, whereas others had a heavy hemorrhagic crust. The intervening skin appeared normal. The palpebral and bulbar conjunctivas were swollen and acutely inflamed, there was a copious purulent conjunctival discharge. The corneas were clear. The anterior nares were reddened and crusted. The lips and the oral mucous membrane were swollen and injected with several denuded and hemorrhagic lesions. The tongue was not involved. The skin about the glans penis was reddened,



FIGURE 1 Photograph on Admission, Showing the Swollen Lids, Encrusted Lips and Erythematous Eruption

and a thick, yellowish exudate was present about the corona and urethral opening. The cervical and axillary lymph nodes were enlarged. The spleen was not palpable.

The rectal temperature was 102.2°F, and the pulse 128. Examination of the blood showed a hemoglobin of 66 per cent and a white-cell count of 4350, with 30 per cent adult neutrophils, 18 per cent young forms, 12 per cent eosinophils, 26 per cent lymphocytes, 8 per cent monocytes and 4 per cent myelocytes. The platelet count was 40,000 by the Rees and Ecker method (normal, over 200,000). Examination of the urine revealed occasional white cells in the sediment. The stools were normal. The blood sulfadiazine level was 2.1 mg per 100 cc. The prothrombin time was normal, as were the coagulation and bleeding times. Clot retraction was complete in 12 hours, and the clot was of fair quality. A Rumpel-Leede test was strongly positive. Agglutination tests for typhoid, paratyphoid and typhus fevers, brucella, infectious mononucleosis and tularemia were negative, as were nasopharyngeal, throat, blood and conjunctival cultures.

During the first 3 days, the conjunctivas were irrigated with boric acid solution, and general supportive care was given, including intravenous fluids and blood transfusions. The conjunctivitis became severer, and pseudodiphtheritic membranes covered the corneas and scleras. These membranes were easily removed with forceps, and the underlying

corneas were clear. Conjunctival culture on the 4th hospital day showed only colonies of hemolytic *Staphylococcus aureus*, and 10,000 units of intramuscular penicillin every 3 hours was begun, penicillin ophthalmic ointment being applied locally. The protective membranes gradually sloughed away during the 2nd week, and both corneas revealed ulcerations that subsequently underwent opacification. By that time, the skin eruption had taken on a purpuric character that was believed to be associated with the thrombopenia (counts of 40,000 to 80,000 platelets). Most of the skin lesions became vesiculated and then ruptured, yielding a clear fluid, after which the layers of skin became adherent and hemorrhagic crusts covered the lesions. The oral mucosa underwent vesicle formation and sloughed, leaving raw areas that bled easily. Cultures of the skin vesicles were repeatedly negative. A light growth of hemolytic *Staph. aureus* was occasionally cultured from the oral lesions. On the 4th day, the spleen was felt to be enlarged. The white-cell count remained below 5000 during the first 2 weeks, and an eosinophil count of 6 to 12 per cent persisted during that time. Stool examinations for parasites were negative. The balanitis had subsided completely by the end of the 2nd week. The crust over the skin began desquamating during the 2nd week, and by the 3rd week, the skin revealed only dark brown patches of pigmentation at the site of the former lesions. The oral mucosa began re-epithelializing and was completely healed by the 3rd week. The platelet counts remained below 100,000 for the most part. Clot retraction and clot quality were impaired in proportion to the thrombocytopenia. An electrocardiogram showed prominent Q waves in the limb leads, with a PR interval of 0.18 second.

The patient was observed for 11 weeks. During that time the skin pigmentation slowly faded. The corneal opacities cleared slightly. The initial course of penicillin was continued through the 11th day and then stopped for 9 days. Penicillin was resumed intramuscularly on the 20th day because of corneal ulceration and continued for 5 weeks. The temperature gradually fell to normal on the 4th day and remained normal during the hospital course. Shortly before discharge the patient developed acute pharyngitis, which cleared rapidly. He was discharged without symptoms, except for slight photophobia and impaired vision, on the 75th hospital day.

On follow up in the ensuing 11 months, the skin pigmentation had gradually faded. The corneal opacities that had encroached on the central vision had remained at about the same density and necessitated placing of the child in a sight-saving class. Visual acuity on July 10, 1946, showed 20/60 bilaterally. Several small adhesions of the palpebral and bulbar conjunctivas remained but did not restrict motility. The platelet counts were normal. The child was in perfect health except for the visual defect.

Although Stevens-Johnson disease has been considered primarily pediatric, approximately a third of the cases reported since 1922 have occurred in patients over fifteen years of age,⁸⁻¹⁰ the case reported by Jones et al.²² having occurred in a fifty-six-year-old woman. The sex incidence is five to one in favor of male patients.

No known etiology for the disease has been established. A virus has been suggested, but no virus has been isolated. Jones and his associates²² examined conjunctival and vaginal scrapings and found no virus inclusion bodies. Their complement-fixation studies of patients' blood with psittacosis antigen showed positive values in dilutions only up to 1:64. Givner and Ageloff¹⁹ found no inclusion bodies in vesicular fluid from skin lesions. Cultures on chick embryos were also negative. Edgar and Syverton¹⁶ injected vesicular fluid intracerebrally and intraperitoneally in rabbits, guinea pigs and mice, with no effects. Chick and Witzberger¹² reported a case and referred to 2 others of Vincent's stomatitis accompanied by erythema multiforme,

MEDICAL PROGRESS

STREPTOMYCIN*

I Bacteriologic and Pharmacologic Aspects

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BOSTON

SEVERAL months have elapsed since streptomycin became available in this country for use in hospitals and then to physicians generally. Heralded at first as the final fruit of victory in the battle against bacterial infections, it seemed to be the obvious and natural supplement to penicillin and was to fill the few gaps among the infections that could not be disposed of by that potent agent. Experiences with penicillin, however, had conditioned the practitioner to expect from streptomycin brilliant, rapid and consistent results in susceptible infections and with essentially no untoward effects.

It soon became apparent, however, that none of these expectations would be entirely fulfilled and that considerable disappointment was inevitable. Streptomycin has, nevertheless, proved to be a useful agent, if properly employed, in certain types of infections. It seems desirable, therefore, to review the available information concerning this antibiotic and to define, so far as that information permits, its field of usefulness and its limitations. The first part of this progress report deals with the properties of streptomycin, its pharmacology and its effect on bacteria in vitro and in experimental infections in animals. The results of its clinical uses in various infections will be considered in the second part.

DISCOVERY AND DEVELOPMENT

Streptomycin is the product of a search by Waksman and his associates^{1, 2} for antagonistic organisms that are active against gram-negative bacteria. Certain actinomycetes, most of them isolated from soils or composts, were found to produce substances possessing marked antibacterial properties, but few of them offered chemotherapeutic potentialities. The first antibiotic that looked promising for the treatment of infections with gram-negative bacteria was streptothricin,^{3, 4} which was active both in vitro

and in vivo. Purified preparations of this substance, however, exerted a delayed toxic effect in animals and, in addition, certain important gram-negative bacilli were found to be naturally resistant to high concentrations.

At the same time, a search was also under way for antibiotics active against acid-fast bacilli. Certain fungi, notably *Aspergillus fumigatus*, were found capable of suppressing the growth of *Mycobacterium tuberculosis*.⁵ Similar groups of organisms were therefore investigated. These combined studies resulted in the isolation of a strain of actinomyces from a heavily manured soil that was similar to one that Waksman had isolated in 1919 and had then classified under the name *Actinomyces griseus*.¹ The antibiotic, produced by the freshly isolated strain in a medium containing meat extract, resembled streptothricin in many respects but differed from the latter in that it had much greater activity against a number of pathogenic gram-negative bacteria and was free of many of its toxic effects in animals. The substance was called streptomycin, the name being derived from the generic designation given to the sporulating and aerial-mycelium producing group of actinomycetes — namely, the Streptomyces.⁶

Other antibiotics have been extracted from *Streptomyces griseus*.⁷⁻¹⁰ One of them has antifungal activity,^{7, 8} and another, called "grisein," has no antifungal properties and a narrower bacterial spectrum than streptomycin.⁹

Only certain strains of *Streptomyces griseus*, however, produce streptomycin.⁹ The composition of the medium is also important.² Among other things, certain organic constituents supplied by the meat extract seem essential, but these can also be supplied by corn steep liquor and some other substances.^{2, 10, 11} Aerated cultures produce maximum growth more rapidly than stationary ones. The medium becomes alkaline during the growth. Growth is terminated at the stage of maximum streptomycin production. The organisms are removed, and the antibiotic is extracted from the clear medium by adsorption on active charcoal. It is then eluted and extracted with suitable solvents and finally concentrated by desiccation in vacuo.² Further treatment is necessary to obtain the pure crystalline product, which is a white powder.^{2, 11, 12}

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A number of contributions may have been overlooked or may not have been available at the time of this writing and many more have appeared since this paper was completed and therefore could not be included.

A case with an erythematous skin eruption, associated with fever, a purulent conjunctivitis, severe stomatitis and balanitis is reported. Corneal ulceration with opacification was the only sequela. The course and clinical picture were almost identical with those in the cases described by Stevens and Johnson.

Persistent leukopenia and thrombocytopenia are reported for the first time in this syndrome.

REFERENCES

- 1 von Hebra F. *On Diseases of the Skin Including the Exanthemata*. 5 vol. London: New Sydenham Society, 1866. Vol. 1.
- 2 Kaposi, M. *Pathologie und Therapie der Hautkrankheiten in Vorlesungen für praktische Ärzte und Studierende*. Fourth edition. 1118 pp. Vienna, 1893.
- 3 Darier, J. A. *Textbook of Dermatology*. 769 pp. Philadelphia: Lea & Febiger, 1920.
- 4 Macleod, J. M. H. *Diseases of the Skin: A textbook for students and practitioners*. 1307 pp. New York: Paul B. Hoeber, Inc., 1921.
- 5 Ormsby, O. S. *A Practical Treatise on Diseases of the Skin for the Use of Students and Practitioners*. Second edition. 1166 pp. Philadelphia: Lea & Febiger, 1921.
- 6 Pusey, W. A. *The Principles and Practice of Dermatology Designed for students and practitioners*. 1021 pp. New York: D. Appleton-Century, 1924.
- 7 Schamberg, J. F. *Diseases of the Skin and the Eruptive Fevers*. Third edition. 585 pp. Philadelphia: W. B. Saunders Co., 1915.
- 8 Stelwagon, H. W. *Treatise on Diseases of the Skin for the Use of Advanced Students and Practitioners*. Third edition. 1115 pp. Philadelphia: W. B. Saunders Co., 1904.
- 9 Stevens, A. M., and Johnson, F. C. New eruptive fever associated with stomatitis and ophthalmia: report of two cases in children. *Am J Dis Child* 24:526-533, 1922.
- 10 Ageloff, H. Erythema multiforme bullosum with involvement of mucous membranes of eyes and mouth (Stevens-Johnson disease): report of case. *New Eng J Med* 223:217-219, 1940.
- 11 Bailey, J. H. Lesions of cornea and conjunctiva in erythema exudativum multiforme (Hebra): report of three cases with grave ocular sequelae. *Arch Ophth* 6:362-379, 1931.
- 12 Chick, F. E., and Witzberger, C. M. Erythema multiforme exudativum accompanying oral Vincent's infection. *Am J Dis Child* 55:573-578, 1938.
- 13 Commission on Acute Respiratory Diseases. Association of pneumonia with erythema multiforme exudativum. *Arch Int Med* 78:687-710, 1946.
- 14 Dugan, J. Erythema multiforme bullosum (Stevens-Johnson disease). *Clin Proc Child Hosp* (Washington, D.C.) 2:298-302, 1946.
- 15 Edgar, K. J., and Syvertson, J. T. Erythema exudativum multiforme with ophthalmia and stomatitis: report of two cases in children with certain observations on histopathology and animal inoculation. *J Pediatr* 12:151-159, 1938.
- 16 Erger, B. D. Erythema multiforme plurifocalis (Stevens-Johnson disease). *Mil Surgeon* 95:308-312, 1944.
- 17 Fletcher, M. W. C., and Harris, R. C. Erythema exudativum multiforme (Hebra) bullous type: cases seen in contagious disease hospital. *J Pediatr* 27:465-479, 1945.
- 18 Ginandes, G. J. Eruptive fever with stomatitis and ophthalmia: atypical erythema exudativum multiforme (Stevens-Johnson). *Am J Dis Child* 49:1148-1160, 1955.
- 19 Givner, I., and Ageloff, H. Stevens-Johnson disease with complete visual recovery. *New York State J Med* 41:1762-1765, 1941.
- 20 Goldfarb, A. A. Case of Stevens-Johnson disease (erythema multiforme bullosum) treated with penicillin. *J Pediatr* 28:579-589, 1946.
- 21 Grossman, E. E. Conjunctivitis associated with erythema multiforme bullosum. *Am J Ophth* 29:1146-1149, 1946.
- 22 Jones, W. Y., Talbot, F. F., and King, W. F. Stevens-Johnson's disease: case report. *Am J Ophth* 29:185-189, 1946.
- 23 Keil, H. Erythema multiforme exudativum (Hebra): clinical entity associated with systemic features. *Ann. Int. Med.* 14:449-494, 1940.
- 24 Kove, S. Stevens-Johnson syndrome (eruptive fever with stomatitis and conjunctivitis). *Am J Med Sci* 210:611-623, 1945.
- 25 Lever, W. F. Severe erythema multiforme: report of two cases of type ectodermis erosiva plurifocalis with development of ocular conjunctivitis and keratitis in one case. *Arch Dermatol. & Syph.* 49:47-56, 1944.
- 26 Levy, A. T. Erythema multiforme bullosum with involvement of mucous membranes of mouth (Stevens-Johnson disease). *J Am. Dent. A.* 30:287, 1943.
- 27 Meisenholder, E. Stevens-Johnson disease: report of case. *Arch. Ophth* 36:631-633, 1946.
- 28 Murphy, R. C. Jr. Eruptive fever involving mouth and eyes (Stevens-Johnson disease): report of case. *New Eng J Med* 230:69-71, 1944.
- 29 Noonin, R. O., and Callaway, J. L. Erythema multiforme and erythema nodosum: comparative study of fifty-four patients. *Arch. Dermatol. & Syph.* 54:560-565, 1946.
- 30 Richards, J. M., and Romaine, H. H. Keratoconjunctivitis sicca: sequela to purulent erythema exudativum multiforme (Stevens-Johnson's disease). *Am J Ophth* 29:1121-1125, 1946.
- 31 Robinson, H. C. Erythema multiforme: report of case of severe erythema multiforme with involvement of mucous membranes treated with penicillin. *Arch Dermatol. & Syph.* 52:91, 1945.
- 32 Rosenberg, L., and Rosenberg, J. Erythema exudativum multiforme (Hebra) with conjunctivitis and stomatitis. *Arch Dermatol. & Syph.* 41:1066-1072, 1940.
- 33 Rutherford, C. W. Membranous conjunctivitis with loss of eyeballs: report of cases. *Tr. Sect. Ophth. A. M. A.*, pp. 169-186, 1929.
- 34 Stanyon, J. H., and Warner, W. P. Mucosal respiratory syndrome. *J. Canad. Med. Assoc.* 3:111-124, 1946.
- 35 Stevenson, J. Erythema multiforme, with unusual manifestations. *J. Oklahoma M. A.* 39:443, 1946.
- 36 Umiker, W., and Crofoot, M. Stevens-Johnson's disease. *U. S. Nav. M. Bull.* 46:1466-1469, 1946.
- 37 Weissberg, A., and Rosen, E. Erythema exudativum multiforme. *Arch. Dermatol. & Syph.* 53:99-106, 1946.
- 38 Wentz, H. S., and Seiple, H. H. Stevens-Johnson syndrome, variation of erythema multiforme exudativum (Hebra): report of two cases. *Ann. Int. Med.* 26:277-283, 1947.
- 39 Wheeler, J. M. Destructive purulent ophthalmia accompanying eruptive fever with stomatitis: report of case. *Am J Ophth* 13:508-514, 1930.

in the assay broth to act as an indicator of bacterial growth. Some authors have advocated the use of the least enriched medium that will give adequate growth.⁵¹

Slide-cell method⁵² The action of streptomycin is observed microscopically by its inhibition of growth of *B. megatherium* in defibrinated blood.

Turbidimetric method Electrophotometric measurement of the turbidity of a staphylococcus culture containing streptomycin has also been used as a basis for assay.⁵⁴

The results of these assays depend not only on variations in the methods used but also on such factors as the type and nutritive value of the medium,^{41 55-55} the salt concentration,^{46 55 59} the hydrogen ion concentration,^{34 46 60 61} the test organism,^{35, 42-45, 49-52} aerobic conditions,³⁶ the size of the inoculum,^{47, 48 60, 62} the time of incubation^{57 62} and factors that inhibit the test organism and are present in the medium^{2 34 37 49 55 56} or in the material being assayed^{49 53 55 63 64}. This last factor may be quite important when *B. subtilis* is used, since it has been shown that a large proportion of human serums inhibit the growth of *B. subtilis* in varying degrees.⁶⁵ This effect may possibly be minimized by the use of citrated plasma instead of serum as in penicillin assay.⁶⁶ Uniform assay mediums have been proposed^{45 49} and are marketed, but their use is by no means universal.

Chemical methods of assay,^{23 67 68} based on the properties of streptomycin or of its degradation products and not necessarily related to antibiotic activity, may have technical usefulness. For the present, however, biologic methods are the most satisfactory for clinical use.

ABSORPTION, EXCRETION AND DISTRIBUTION

Absorption

Blood levels following intravenous and intramuscular administration of streptomycin have been extensively studied in man^{44 45 69-75} and in animals^{47 76-78}. In general, maximum levels are attained a few minutes after intravenous injection, whereas after intramuscular injection of the same dose there is a gradual rise to a maximum in one or two hours.^{69 72 73} At that time the levels are approximately the same for either method of administration, and there is a gradual falling off, with some evidence that the levels from the intramuscular injections are somewhat better sustained.^{72, 73} The levels attained and the duration of detectable activity in the blood serum depend on the size of the dose, but are not directly proportional to it.⁷² Table 1 shows serum levels attained at different times after various doses. These figures agree in the main with those reported by others, most of whom used similar assay methods — variations of the technic described by Stebbins and Robinson.⁴²

Subcutaneous injections have not been widely used in human beings, but levels may be obtained

that are only slightly lower than those following intramuscular administration.^{69 71, 73} Measurable levels of streptomycin may still be present in the blood twelve hours after a single injection of 200,000 units,⁷³ but therapeutic levels cannot be relied on after six hours in a normal subject.

Intermittent injections of suitable doses by any of these three parenteral routes every four to six hours will ensure the maintenance of desired levels. There may be some build up of levels after the first

TABLE 1 Serum Concentrations in Man after Various Doses of Streptomycin *

Dose units	TIME AFTER INTRAVENOUS OR INTRAMUSCULAR DOSE		
	1 hr	2 hr	4 hr
2,000-50,000	1-5-2-5	1-0-2-5	0
200,000	10	6	3
400,000	10-15	8	6
500,000	15-20	15-20	10-15
1,000,000	25-50	25-45	15-25

*From Buggs et al.⁷²

few successive injections.^{69 70 72} An attempt to slow absorption from intramuscular injections by the use of streptomycin in beeswax and peanut oil or Solvecillin (a water-in-oil emulsion) gave inconclusive results.⁷⁹

When streptomycin is given orally only small amounts appear in the blood and urine.^{44, 45 47, 69-71, 72 78} The fecal concentration after oral administration is high,^{44 69} and almost all the administered streptomycin is recoverable in the feces, indicating that failure to enter the blood stream from the gastrointestinal tract is due to poor absorption rather than to destruction.⁴⁵ Artificial gastric or duodenal juice does not inactivate streptomycin.⁷⁰

An appreciable concentration of streptomycin is still present in the cerebrospinal fluid twenty-four hours after an intrathecal injection of 20,000 units.⁷⁰ Similar results have been obtained by many workers.^{71 72 80 81}

Few reports are available on the absorption of streptomycin given as an aerosol. Detectable amounts are not present in venous blood, and only small amounts are found in the urine after inhalation of 200,000 units or less.^{71 73 82} In a patient receiving 500,000 units daily, 6 per cent of the administered dose was found in the twenty-hour urine.⁷¹

Excretion

The bulk of the streptomycin excreted following parenteral administration is found in the urine, only a small fraction — 6 per cent or less — being found in the stools.^{45 69} Streptomycin has been recovered as an active colorless solid from the urine of dogs, according to Tennant, cited by Robinson.⁸³ Excretion in the urine is greatest during the two hours following a single intravenous or intramuscular

CHEMICAL PROPERTIES

ASSAY

Streptomycin was early recognized to be an organic base.² Crystalline reineckates were soon obtained, and tentative empirical formulas were derived from analyses of these salts.¹⁴⁻¹⁶ Some studies of its structure have shown that it is composed of two main portions¹⁷⁻²¹ streptidine ($C_8H_{14}O_4N_6$), a basic substance, and streptobiosamine ($C_{13}H_{21-23}O_5N$), a nitrogen-containing disaccharide to which streptidine is joined through a glucoside linkage, which is readily split by methanolic hydrochloric acid.¹⁷ Further information concerning the composition and structure of streptidine^{18, 20-22} and the degradation products of streptobiosamine²²⁻²⁵ has been revealed, but the final elucidation of the structure of streptomycin and its synthesis remains to be accomplished.

Streptomycin is a hygroscopic, optically active,¹² organic base, soluble in water but insoluble in the usual organic solvents. It forms salts with acids, and of these the soluble hydrochloride and sulfate are used clinically. The relatively insoluble helianthate is used in some methods of purification,¹² and the crystalline reineckate has been utilized for its characterization.¹⁴ It is adsorbed on charcoal in alkali and may be eluted by acid.^{2, 26, 27}

Streptomycin reacts with a number of carbonyl reagents.¹⁷ It is readily oxidized to inactive streptomycinic acid by bromine.²² Catalytic reduction by hydrogen results in dihydrostreptomycin,²⁸⁻³⁰ which is a substance having antibiotic activity of the same order as streptomycin but which, in contrast to it, does not lose activity in the presence of cysteine or carbonyl reagents and is also stable at a higher hydrogen ion concentration.²⁹ Streptomycin reacts with alkaline copper solutions, urines containing 1000 units or more reduce Benedict's solution.³¹

STABILITY

Streptomycin is a relatively stable substance. Commercial samples containing less than 1 per cent of moisture show no loss of potency when stored at room temperature for a year.³² It is also stable in solution at ordinary temperatures, there is no loss of activity in solutions at or below 28°C at pH 3 to 7 over a period of sixty days, whereas it requires thirty-seven hours at 95°C to reduce the activity of a solution at pH 5.5 to a half.³² Buffered solutions containing 100 and 1000 units per cubic centimeter at pH 6.0, 7.0 and 8.0 are stable over a period of three months at 10°C.³³ Heating at 70°C for thirty minutes produces no appreciable loss of activity.^{34, 35} Less than 50 per cent loss occurs on heating at 100°C for 10 minutes.³ A marked increase in alkalinity causes rapid destruction, and boiling with normal sodium hydroxide for ten minutes results in complete inactivation.³³ No biologic agent or enzyme system has yet been found capable of destroying streptomycin.³⁶

Units

Amounts of streptomycin are now expressed in terms of the weight of the pure base in grams, milligrams or micrograms.³⁷ Waksman³⁸ originally measured streptomycin in units, the unit being defined as the minimal amount of streptomycin activity that must be present in 10 cc of nutrient medium to inhibit the growth of a given strain of *Escherichia coli*, this has also been called the "*Esch coli* unit" or "S unit," which is approximately equivalent to 10 microgm.* He also proposed two other units: an "L unit," to indicate 1,000,000 S units, and a "G unit," to represent 1000 S units. These designations are no longer widely used. Commercial streptomycin is provided as the hydrochloride or sulfate, but the potency is expressed in terms of the weight of the pure base.⁴⁰

Methods

Procedures that depend on the antibacterial properties of streptomycin have been widely used and form the basis of all the reported quantitative studies in patients. Most of them employ the same principles that are used in penicillin assay, with variations in the mediums and test organisms to suit the properties of streptomycin.

Streak-plate method.⁴¹ This is a crude method that consists in the incorporation of graded dilutions of the material being tested in nutrient agar, followed by streaking of the surface with an array of organisms of known and graded sensitivity.

Agar-diffusion methods. These are modifications of the cylinder-plate technique⁴² described for penicillin assay, and two main types are used. The first comprises the cup method, in which the material being assayed is placed in cups arranged on the surface of suitable agar plates seeded with a test organism. Stebbins and Robinson⁴³ used *Staphylococcus aureus* as the test organism. This procedure has been widely used and modified, and other test organisms — notably *Bacillus subtilis*^{44, 45} — have been proposed. The second is the paper-disk method, which is a further modification of the first type, in which the assay cylinders are replaced by small paper disks moistened with the solutions being assayed.^{46, 47}

Broth-dilution methods. Serial dilutions, usually twofold, are set up as in the penicillin assay method described by Rammelkamp.⁴⁸ The organisms generally used have been strains of *Klebsiella pneumoniae*,⁴⁹⁻⁵¹ *B. circulans*⁵² and *Staph. aureus*,⁵³ and the inoculum is between 1000 and 100,000 organisms per cubic centimeter. End-points have been determined by turbidity or subculture, or both, on nutrient agar with or without inclusion of blood.

*It is well to bear in mind that this unit has no relation to that of penicillin. The original Oxford unit of penicillin was defined as the amount required to inhibit 50 cc of a staphylococcus culture. The international unit of penicillin is now defined as 0.6 microgm of pure penicillin G.⁵⁴

duction of acid³⁶ When a glycine buffer of pH 8 is present, no inactivation occurs Glycine itself has no demonstrable effect on streptomycin³⁶

Effect of aerobic and anaerobic conditions The action of streptomycin on facultative anaerobes is reduced if they are grown in an atmosphere of hydrogen or nitrogen instead of air and is almost completely abolished in carbon dioxide These changes are related to the reaction and are prevented, in carbon dioxide, by the addition of potassium bicarbonate to the agar³⁶

Inactivation by chemical substances The inhibitory and inactivating effect of a number of chemical substances has been studied^{17, 36, 93-96} Cysteine inactivates streptomycin, and this effect is reversible by iodine⁹³ Among other substances tested 2-aminoethanediol caused inactivation⁹³ Thioglycolic acid may also cause inactivation,^{36, 96} but this may be due to the presence of glucose in the thioglycollate medium³⁶ or to an effect on the oxidation-reduction potential⁹⁵ Among oxidizing and reducing agents that have been tested potassium permanganate and potassium periodate were the most effective in destroying the antibiotic activity of streptomycin⁹⁵ Vitamin C⁹⁵ and carbonyl compounds¹⁷ such as hydroxylamine, semicarbazide, phenylhydrazine and methylphenylhydrazine, may reduce its activity About 98 per cent inactivation is attainable at pH 5.5 with semicarbazide, and this substance has been proposed for use in the sterility testing of concentrated streptomycin solutions⁹⁷

Effect of body fluids The action of streptomycin on staphylococci was not appreciably influenced by various body fluids, pus or normal tissue juices⁶¹ Incubation of the drug with artificial gastric or duodenal juice had no appreciable effect on its activity⁷⁰ Defibrinated blood and normal urine, likewise, did not decrease the activity⁵⁸ Some reduction in activity was noted, however, in human serum.⁵⁵ The effect varies with the organism and with the concentration of the serum Serum may enhance the activity of streptomycin against *Escherichia coli*⁶⁴ or *K pneumoniae*,⁴⁹ whereas it inhibits this action against various organisms including *Staph aureus* and *Streptococcus haemolyticus*,^{63, 64} and it does not affect the sensitivity of *Brucella*⁶³ Possibly, these conflicting results are due to differences in the methods used Their clinical significance is not clear

MECHANISM OF ACTION

Streptomycin is generally bacteriostatic for susceptible organisms in low concentrations and bactericidal at higher levels^{2, 93-101} Microscopical examinations of organisms growing in subinhibitory levels of streptomycin have shown morphologic changes¹⁰² Large bizarre forms were noted in the study of *Eberthella typhosa*¹⁰⁴ and *Pasteurella tularensis*,¹⁰⁵ whereas marked elongation was noted with *Shigella sonnei* and to a lesser extent with

Salmonella typhimurium, *Aerobacter aerogenes* and *Proteus ammoniae*¹⁰¹ Streptomycin has a bactericidal action both on growing cultures and on resting or nonmultiplying cells,^{100, 101, 106} although this may not be true of its action on tubercle bacilli¹⁰⁷ This bactericidal action is more marked against young

TABLE 2 Sensitivity of Various Organisms to Streptomycin

ORGANISM*	REPORTED SENSITIVITY RANGE	MOST FREQUENT
<i>Actinomyces visus</i> ¹⁰⁸	0.5-125	6-27
<i>Aerobacter aerogenes</i> ¹⁰¹	0	
<i>Bacillus anthracis</i> ¹⁰⁹	0	
<i>Bacillus cereus</i> ¹¹⁰	0.8-2	
<i>Bacillus megaterium</i> ¹¹¹	0.2-1	
<i>Bacillus subtilis</i> ¹¹²	0.1-125	1-5
<i>Brucella abortus</i> ¹¹³	0.1-1	
<i>Brucella melitensis</i> ¹¹⁴	0.1-1	
<i>Brucella suis</i> ¹¹⁵	0.1-1	
<i>Clostridium perfringens</i> ¹¹⁶	>104	
<i>Clostridium septicum</i> ¹¹⁷	>10	
<i>Clostridium tetani</i> ¹¹⁸	>10	
<i>Clostridium botulinum</i> ¹¹⁹	>104	
<i>Clostridium histolyticum</i> ¹²⁰	>100	
<i>Corynebacterium diphtheriae</i> ¹²¹	0.1-1	
<i>Diphtheria</i> ¹²²	4-50	
<i>Diphtheroides</i> ¹²³	1-125	
<i>Enterobacteriaceae</i> ¹²⁴	1-120	1-16
<i>Escherichia coli</i> ¹²⁵	0.1-1	
<i>Haemophilus ducreyi</i> (chancroid) ¹²⁶	0.1-1	<5
<i>Haemophilus influenzae</i> ¹²⁷	0.1-1	
<i>Haemophilus parainfluenzae</i> (Pleiffer's bacilli) ¹²⁸	1-10	1-5
<i>Haemophilus parvus</i> ¹²⁹	2-5	
<i>Haemophilus pyrus</i> ¹³⁰	1-17	1-
<i>Histoplasma capsulatum</i> ¹³¹	>2500	
<i>Klebsiella pneumoniae</i> ¹³²	0.2-1.5	
<i>Klebsiella terrigena</i> (Friedlander's bacilli) ¹³³	0.2-125	0.6-8
<i>Listeria monocytogenes</i> ¹³⁴	2-5	
<i>Malleomyces mallei</i> (glanders) ¹³⁵	10-100	
<i>Mycobacterium tuberculosis</i> (avian) ¹³⁶	10-50	
<i>Mycobacterium tuberculosis</i> (human and bovine) ¹³⁷	0.1-1	
<i>Nisseria catarrhalis</i> ¹³⁸	1-4	
<i>Nisseria gonorrhoeae</i> (gonococcus) ¹³⁹	5-40	10-15
<i>Nisseria intracellulare</i> (meningococcus) ¹⁴⁰	1-40	
<i>Nocardia</i> ¹⁴¹	4-12.5	
<i>Pasteurella pestis</i> (plague) ¹⁴²	0.5-1.5	
<i>Pasteurella tularensis</i> ¹⁴³	0.1-0.5	
<i>Paracolon bacillus</i> ¹⁴⁴	2-128	2-16
<i>Proteus morganii</i> ¹⁴⁵	1-128	5-50
<i>Proteus vulgaris</i> ¹⁴⁶	0.4-128	4-25
<i>Pseudomonas aeruginosa</i> (Bacillus pyocyaneus) ¹⁴⁷	2-200	8-50
<i>Salmonella</i> (various species) ¹⁴⁸	4-120	4-32
<i>Serratia lutea</i> ¹⁴⁹	0.25	
<i>Serratia marcescens</i> (Bacillus prodigiosus) ¹⁵⁰	1-64	
<i>Shigella</i> (various species) ¹⁵¹	0.2-8	3-7
<i>Staphylococcus albus</i> ¹⁵²	1-256	1-4
<i>Staphylococcus aureus</i> ¹⁵³	0.5-128	1-5
<i>Streptococcus faecalis</i> ¹⁵⁴	12.5-60	
<i>Streptococcus haemolyticus</i> ¹⁵⁵	1-128	2-32
<i>Streptococcus nonhemolyticus</i> ¹⁵⁶	1-128	1-32
<i>Streptococcus mitis</i> ¹⁵⁷	0.1-128	1-12
<i>Streptomyces</i> (various species) ¹⁵⁸	0.4-12.5	
<i>Vibrio cholerae</i> (cholera) ¹⁵⁹	5-100	

* A few additional organisms are listed by Waksman and Schatz¹⁶⁰ and by Pulaski and Sprinz¹⁶¹ Additional fungi are mentioned by Robinson¹⁶² and Reilly¹⁶³

[†] Minimum inhibiting concentration of streptomycin in micrograms per cubic centimeter of culture

cultures than against older ones³⁶ Streptomycin has no effect on tetanus toxin¹⁰³

There is as yet no clear evidence to indicate just how streptomycin acts Some antibiotics are adsorbed on the surface of bacterial cells, but this is apparently not true with streptomycin, at least so far as *B subtilis* and *Staph aureus* are concerned⁹⁵ It has been suggested that streptomycin acts by the combination of its guanido groups with

injection, up to 65 per cent is excreted in twelve hours, and 9 per cent more may appear during the following twelve hours.⁷³ The amount excreted in twenty-four hours is variously estimated as representing 17 to 90 per cent of the administered dose,⁷⁷ with averages of 57 to 66 per cent.⁶⁹ Only negligible amounts are recoverable from the urine after twenty-four hours.⁴⁴ ⁶⁹ ⁷¹ Streptomycin is concentrated by the kidney, and high urine levels are easily attainable with therapeutic doses. The levels depend largely on the volume output of urine and have ranged from 120 to 2000 units per cubic centimeter,⁵⁰ ⁶⁹, ⁷¹ ⁷³ ⁸⁴ ⁸⁵ and even over 4000 units per cubic centimeter have been reported.³¹, ⁸⁶ The renal clearance of streptomycin has been studied, and the drug was found to be excreted by the glomeruli alone, 38 to 67 cc of plasma being cleared per minute.⁷² There may be diminished excretion and consequent concentration in the blood in patients with severe renal damage.³¹, ⁷², ⁸⁶

Distribution

Following parenteral injection streptomycin is found in most of the body fluids and tissues. Concentrations are higher in the kidney than in the blood.⁵⁸ ⁷³ The findings in other organs are irregular.⁴⁷ ⁵³ ⁷² ⁸⁷ and probably unreliable. In mice, high concentrations are found in the liver and spleen if the streptomycin is given with trypan blue.⁸⁷ No demonstrable streptomycin was present in red cells hemolyzed by freezing, although the plasma removed from the same sample of blood showed a good level.⁷² Streptomycin was not found in pus from soft-tissue abscesses in 4 cases.⁵³

Spinal fluid Most authors failed to demonstrate significant amounts of streptomycin in the cerebrospinal fluid even after large intravenous or intramuscular doses, when there was no meningeal inflammation,⁶⁹ ⁷¹⁻⁷³ although 1 to 5 units per cubic centimeter may be found in the cerebrospinal fluid of patients with meningitis following similar injections.⁶⁹⁻⁷³

Pleural fluid Levels found in the pleural fluid of patients with effusions, although somewhat lower,⁵³ may be better sustained than those attained in the blood.⁶⁹ ⁷³ The appearance of streptomycin in pleural fluid is apparently slower if the fluid is thick.

Peritoneal fluid The drug is found in the peritoneal fluid following parenteral administration, and the concentrations are usually less than those in the blood.⁵³ ⁶⁹ ⁷² ⁷³ Whereas most of the studies were made on patients with ascites, it has been shown that the agent readily enters the peritoneal fluid of normal dogs and of dogs with acute diffuse peritonitis.⁸⁸ Doses of 500,000 to 600,000 units intravenously or intramuscularly result in peak levels of 15 to 33 units per cubic centimeter.⁸³

Bile Numerous studies have been made on the presence of streptomycin in bile.⁵³ ⁶⁹ ⁷¹ ⁷³ ⁸⁹ ⁹⁰ The drug was found in the bile only when the

cystic duct was patent. It does not seem to be concentrated by the liver, and levels in the bile are lower than those found in the blood. Impaired liver function results in lower levels or even absence of streptomycin in the bile. There is no evidence of absorption or concentration in the gall bladder.

Ocular fluids In rabbits, good levels were readily achieved in the conjunctiva, sclera, extraocular muscles and aqueous humor following intravenous administration. Higher concentrations were attainable in secondary aqueous. Penetration to the aqueous was not accomplished by local instillations unless the cornea was damaged. High concentrations could be obtained by iontophoresis.⁹¹ In a case of glaucoma⁸⁹ the secondary aqueous showed higher levels than the aqueous.

Fetal blood and amniotic fluid Streptomycin readily passes through the placenta and is found in the fetal circulation.⁷¹ Levels in umbilical-cord blood and amniotic fluid were approximately half those found in the maternal blood taken at the same time. Only negligible amounts were detected three hours after injection of the mother.⁹²

FACTORS INFLUENCING ACTION OF STREPTOMYCIN IN VITRO

Effect of reaction and number of organisms The antibiotic effect of streptomycin is greater in an alkaline than in an acid medium.³¹ ⁴⁶ ⁶⁰ ⁶¹ In addition, streptomycin activity is considerably decreased if the size of the inoculum is sufficiently increased.⁵⁷ ⁵⁸ ⁶⁰ ⁶² With an inoculum of 5000 or 10,000 organisms per cubic centimeter there may be a fourfold loss of activity with a change in reaction from pH 7.2 (at which activity is usually estimated) to pH 6.2 (a fairly usual reaction for pus). If, in addition, the inoculum is increased a thousandfold, the same change in reaction will decrease the activity sixteen to thirty-two times.⁶⁰ The effect of acidity is not due to destruction of streptomycin, since it can be restored by upward adjustment of the reaction.⁶¹ These two factors may have contributed to some of the failures of streptomycin, as in cases of walled-off collections of pus.⁷⁴

Effect of salts The addition of many salts, such as sodium chloride, acetate and bicarbonate, potassium chloride and bicarbonate, lithium chloride and sulfate and some phosphates, has been found to increase the effect of streptomycin against *B. subtilis*.⁴⁶ Others,⁵⁸ ⁵⁹ however, noted a reduction in effect on certain organisms in the presence of increased salt concentrations, but their observations were made under different conditions. The salts in normal urine did not decrease streptomycin activity.⁵⁵

Effect of glucose Glucose reduces the activity of streptomycin.² ³⁴ ⁶⁶ The potency of streptomycin in agar is reduced to a half in the presence of 2 mg in 10 cc. This effect is probably related to the pro-

Spirochetal infections A considerable therapeutic effect was noted against *Borrelia nocy* (one of the organisms of relapsing fever) in mice and *Leptospira icterohaemorrhagiae* (the etiologic agent in Weil's disease) in Syrian hamsters, the effect in these infections, however, was less than that produced by penicillin.¹⁶⁴ A suppression of the infection in rabbits was caused by the Nichols strain of *Treponema pallidum* after prolonged therapy with large doses (200,000 units a day),¹⁶⁵ ¹⁶⁶ but lower doses failed to suppress the infection.¹⁶⁷ ¹⁶⁸

Fungous infections Streptomycin was ineffective against *Blastomyces dermatitidis* infections of chick embryos.¹⁶⁹

Virus and rickettsial infections Streptomycin failed to affect the multiplication of a number of strains of influenza A and B viruses¹⁷⁰ ¹⁷¹ and the viruses of psittacosis¹⁷⁰ and meningopneumonitis¹⁷¹ in chick embryos. It was ineffective in the prophylaxis and treatment of experimental vaccinia in rabbits.¹⁷² It was more active than penicillin against *Donausia granulomatis* in embyonated eggs.¹⁷² Feline pneumonitis was not suppressed by streptomycin in vitro or in vivo.¹⁷³ In doses of 2 mg per egg it suppressed the growth of the rickettsias of epidemic (louse-borne) and endemic (murine) typhus fever in chick embryos but had no effect against that of scrub typhus fever in the same amounts.¹⁷⁴ It also suppressed the growth of the virus of lymphogranuloma venereum in eggs.¹⁷⁵

Protozoal infections No action was noted against *Plasmodium cathamerum* in canaries¹⁷⁶ or *P. lophurae* in ducks.¹⁷⁷ ¹⁷⁸ A slight suppressive action was noted against *P. gallinacium* in chicks.¹⁷⁹

LABORATORY USES

Streptomycin has been used either alone or in conjunction with penicillin or sulfonamides, or both to prevent contaminations by susceptible organisms in the course of isolation of various infectious agents,¹⁷⁶ ¹⁷⁷ including viruses¹⁷⁶ ¹⁷⁷ and protozoa.¹⁸⁰ ¹⁸¹ It has no effect on the embryo of the developing hen's egg, at least in the concentrations that have been used.¹³⁶ ¹³⁷ ¹⁴⁸ ¹⁷⁶ ¹⁷⁷

TOXICITY IN ANIMALS

A great deal of work has been done concerning the toxicity of streptomycin for animals, most of it by Molitor and his co-workers.³⁷ Administration of the drug produces acute and chronic toxic reactions, some of which deserve special mention.

Acute Toxicity

The toxicity of purified specimens of streptomycin is extremely low.² ³⁷ ¹⁰² Acute toxicity in mice was evidenced by increased activity, dyspnea and respiratory failure. The LD₅₀* for mice, determined on two hundred lots of streptomycin, ranged from 350 to 700 mg per kilogram of body weight in

*Smallest amount killing 50 per cent of the animals within the test period.

most cases. Differences in toxicity could not be correlated with the potency of the preparations studied. The LD₅₀ for eight samples of highly purified streptomycin ranged from 75 to 300 mg per kilogram of body weight when given intravenously and from 300 to 1250 mg when given subcutaneously — a ratio of about 4:1. The LD₅₀ for guinea pigs was 400 mg per kilogram of body weight for a batch whose LD₅₀ for mice was 600 mg.³⁷ Similar values in guinea pigs have been obtained by others.¹⁶¹ Subcutaneous injection of 30 to 70 mg per kilogram of body weight produced acute respiratory distress in monkeys.³⁷ Mice survived oral administration of 5000 mg of pure streptomycin per kilogram of body weight, whereas doses of 1000 to 3000 mg of crude concentrates per kilogram of body weight proved fatal.³⁷

Chronic Toxicity

Mice receiving up to a total of 1000 mg per kilogram of body weight subcutaneously in six days appeared normal, as did rats after seventy-two days on 100 mg daily and guinea pigs on amounts up to 60 mg per day. No pathologic changes were noted in these animals.³⁷ ^{184†}

Rats developed nutritional deficiencies when fed large doses of streptomycin and purified diets for prolonged periods¹⁷⁸ but not with smaller doses¹⁷⁸ or when the diet contained essential growth factors.¹⁷⁹ The picture presented, which was similar to that observed in experimental biotin deficiency, responded to biotin therapy.¹⁷⁸ The bacterial content of the feces of these animals was markedly reduced.

Monkeys given large doses parenterally — 50 to 100 mg per kilogram of body weight — exhibited proteinuria, and some showed bromsulfalein retention. Autopsies revealed a peculiar type of fatty infiltration of the kidneys and less often of the liver. There was evidence that this process is reversible.³⁷ Dogs given 50 to 100 mg showed protein, casts and cells in the urine after one and a half to two weeks. Three of the dogs developed changes in gait and posture suggestive of labyrinthine or cerebellar disturbance,³⁷ a phenomenon that has also been noted in human beings.^{180, 181} No obvious pathological changes were found in the central nervous systems of these dogs.¹⁸²

An investigation of the antidiuretic properties of streptomycin was carried out following a report of urinary retention in man occurring after administration of the drug.¹⁸³ It was shown that this effect was associated with impurities but that pure streptomycin had no such effect.³⁷

Local Effects

Instillation of a solution of streptomycin caused reddening of a rabbit's eye,³⁷ ¹⁸⁴ but this disappeared within twelve to twenty-four hours when the solu-

†Slanetz (Proc Soc Exper Biol & Med 63:451-453, 1946) observed no toxic effects in mice fed up to 1000 mg daily but a greater increase in weight occurred in second litters at higher dosage levels as compared with controls.

nucleic acid¹⁰⁹ Another possibility is that streptomycin acts by coupling with thiol groups that are biologically essential to the bacterial cells⁹⁴

EFFECT IN VITRO AND IN EXPERIMENTAL INFECTIONS

In Vitro

Streptomycin has been shown to be bacteriostatic and bactericidal in vitro for a large number of gram-negative and gram-positive bacteria and for *Mycobacterium tuberculosis*. The range of sensitivity of a variety of organisms is presented in Table 2. Streptomycin is ineffective or has a limited effect against some spores,¹⁰⁰⁻¹⁰³ and the gram-positive spore-forming pathogenic anaerobes are resistant,¹⁰² as are most of the fungi,^{7, 102-103, 113-122} viruses¹³⁶⁻¹³⁸ and protozoa¹³⁹⁻¹⁴² that have been studied. Another antibiotic isolated from streptomycin-producing strains of *Streptomyces griseus* exerts an antifungal effect on *Cryptococcus neoformans* and on some nonpathogenic strains.⁷⁻⁸

In a consideration of the probable effectiveness of a chemotherapeutic agent against a particular micro-organism, it is customary to include the sensitivity or susceptibility of the organism to the agent in vitro and the effect of the agent on the course of experimental infections in suitable animals.

Sensitivity in vitro is usually expressed as the minimum effective or inhibiting concentration (M E C or M I C), and this is determined by a suitably devised experiment in which large numbers of organisms are pitted against various concentrations of streptomycin in a medium suited to the growth requirements of the organism. Such factors as reaction, size of inoculum, time of incubation and use of solid or liquid mediums vary according to circumstances and from worker to worker. Thus, it is difficult to compare the reported sensitivities obtained from different laboratories. Furthermore, since it has been shown that different strains of the same bacterial species may vary greatly in their susceptibility to streptomycin and since sensitivities are usually determined on material obtained by a single colony selection,* the figures can be accepted as showing merely the range or order of sensitivity. Some organisms such as *Pasteurella tularensis* and *Mycobacterium tuberculosis* are extremely sensitive, whereas others, such as *Pseudomonas aeruginosa*, may be just within the limits of the streptomycin levels attainable in the body.

Therapeutic correlations Some aspects of the correlation of in vitro sensitivity with the therapeutic value of streptomycin based on observations with *Haemophilus influenzae* are discussed by Alexander.⁵⁷ She suggests that sensitivity figures show the best agreement with therapeutic results if they are obtained by the use of large inoculums, mediums

designed for optimal growth and an adequate growth period. An unpredictable factor involved in the lack of such a correlation is the emergence of resistant strains during treatment. There are others, as evidenced by the fact that treatment of infections in man due to various strains of *Brucella* and *Salmonella* and to *E. typhosa* have been disappointing despite apparently favorable in vitro sensitivity values, adequate blood levels and failure to demonstrate the development of resistance.^{45, 62, 145}

Experimental Infections

Bacterial infections The protective action of streptomycin, in adequate dosage, for experimentally infected animals has been demonstrated with staphylococci,¹⁰² pneumococci,¹⁰² species of *Salmonella*,^{102, 146} *H. influenzae*¹²⁰ and meningococci.¹²⁷ The drug has been used for clearing mouse colonies of *Salmonella* infections.¹⁴⁷

The results in certain experimental infections are of interest. In experimental typhoid infections in mice the mortality rate was higher among infected animals receiving small doses of streptomycin than in similarly infected controls. Larger doses, however, were protective.¹⁰⁴ Infections with *Brucella abortus* in chick embryos were controlled,¹⁴⁸ and those in most guinea pigs were eliminated if adequate streptomycin therapy was instituted within a week.¹¹² Infections with *S. schottmülleri* and *P. aeruginosa* in mice, with *S. gallinarum* in chick embryos and *Proteus vulgaris* in animals were also prevented.¹⁴⁸ Chick embryos were also protected against *Pr. vulgaris* infections.¹⁴⁸ The course of infection in mice with *Pasteurella pestis* was favorably influenced, and the streptomycin effect was similar to that produced by sulfadiazine.^{128, 149} Streptomycin protected mice completely against fatal doses of *P. tularensis*.^{129†} Some protective therapeutic effect was noted against *H. pertussis* in mice.^{151, 150}

Streptomycin prolonged the life of mice experimentally infected with *Clostridium perfringens*.¹⁵¹ Streptomycin resulted in the survival of 92 per cent of mice infected with anthrax as against 58 per cent with penicillin and 5 per cent with sulfadiazine.¹⁵² There was only a slight effect on *Erysipelothrix rhusiopathiae* (erysipeloid) infections in mice—much less than that with penicillin.¹⁵³ Streptomycin seemed to be chemotherapeutically active against infections in rats with pleuropneumonia-like organisms and was more effective than gold compounds in the treatment of the associated arthritis.¹⁵⁴

Extensive studies on experimental infections caused by *Mycobacterium tuberculosis* have been carried out in guinea pigs,^{155, 156-157} mice^{158, 159} and chick embryos.¹⁶⁰ Streptomycin was shown to exert a marked suppressive effect on experimental tuberculosis in these animals. Combined therapy using streptomycin with Promin^{161, 162} or with Diasone¹⁶³ gave better results than any of these agents used singly.

*Infected urines or exudates may be planted directly on suitable agar plates containing graded concentrations of streptomycin, and the sensitivity of the infecting bacteria can thus be determined more promptly.¹⁴³ *In vivo* sensitivity test employing the chick embryo has also been

†The effect varies with the dose and time of institution of therapy. Latent infection without development of resistance is demonstrable in some surviving mice.¹⁵⁰

Morphologic and Cultural Properties of Resistant Bacteria

No changes were noted in the morphology of cells or colonies of gonococci or meningococci that had become resistant in vitro.¹²⁷ Loss of pigmentation and a reduction in the rate of carbohydrate fermentation were noted in two resistant strains of *Staph aureus*.¹⁹⁰ Changes in colony forms have been noted in strains cultivated from urinary-tract infections that had become resistant during treatment. Some species of *Proteus* lost their spreading property.¹⁹¹ A number of strains of *Shigella* showed atypical reactions in Russell's double-sugar medium after becoming resistant, but this aberration disappeared during the course of five to seven transfers through streptomycin-free mediums.⁵⁹

Two strains of *K. pneumoniae* that had become resistant on repeated passage through streptomycin-containing liquid mediums failed to ferment saccharose or to grow on citrate mediums. The ability to ferment saccharose returned in one of these strains after repeated transfer through streptomycin-free broth. Corresponding strains that had developed resistance during treatment and those in which resistance was rapidly enhanced by serial transfers on solid mediums containing streptomycin did not show these changes.¹⁹¹ Resistant strains of *Esch coli* do not synthesize biotin so well as sensitive strains.¹⁷⁶

One strain of *Brucella* that had become resistant during treatment showed two distinct forms: one grew fairly rapidly as a large colony but lost its characteristic biochemical reactions, the other grew slowly, formed smaller colonies, was more highly resistant and largely retained its morphologic and biochemical reactions. The former also showed some changes in morphology and staining properties as compared with the original sensitive strain. Growth of the resistant strain but not the sensitive ones was stimulated by sublethal concentrations of streptomycin.⁶²

All these changes were much less striking than those observed in organisms becoming resistant to penicillin.⁶² 195-197

Persistence of Acquired Resistance

Present evidence suggests that resistance once acquired, is usually a fairly stable property. Gonococci and meningococci that had acquired resistance by exposure to streptomycin in vitro retained their resistance over a period of three and a half months.¹²⁷ Five strains of *Shigella* remained resistant to over 1000 units per cubic centimeter when stored for six months at 4°C,⁵⁹ and the same strains retained appreciable resistance after fifty transfers, although there was a distinct falling off in the resistance of some. Similar results were obtained with a series of strains having somewhat lower levels of resistance.⁵⁹ Strains of staphylococci showed some decrease in resistance after transfer through broth,¹⁹⁰ whereas strains of *Staph aureus*

resistant to 2500 units per cubic centimeter retained their ability to grow well in 1000 units per cubic centimeter after four months in the refrigerator after several mouse passages and after being adapted to penicillin.⁶¹ Strains of *Mycobacterium tuberculosis* made resistant in vitro retained that resistance after repeated subculture in streptomycin-free mediums for four months.¹⁰⁷ Those obtained from patients under treatment remained resistant after residence in guinea pigs for ten weeks or more.¹⁹³ The resistance of a strain of *H. influenzae* was reduced considerably on subculture in streptomycin-free Leventhal broth.¹²⁰ The strain of *Br. abortus* referred to above retained its resistance during transfer in streptomycin-free mediums for three months.⁶² Strains from urinary infections that became resistant during treatment have retained the same degree of resistance after a hundred transfers in a streptomycin-free medium.¹¹⁷

Reciprocal Sensitivity (Cross Resistance)

Organisms becoming resistant to one antibiotic may remain sensitive to another.⁹⁹ When *Staph aureus* was made resistant to penicillin, streptomycin or streptothricin, a slight increase in resistance to streptomycin was noted in the organisms becoming resistant to streptothricin,¹⁵⁹ but no other reciprocal or cross resistance has usually been noted.⁶¹ 159 In one study, however, it was noted that two of five strains of staphylococci developing resistance to penicillin increased in resistance to streptomycin, whereas five strains becoming fast to streptomycin remained sensitive to penicillin.¹⁹⁰ Streptomycin-resistant meningococci are susceptible to penicillin in vivo and in vitro, and meningococci made resistant to penicillin remain susceptible to streptomycin.¹²⁷ Gonococci that acquired resistance to either agent remained susceptible to the other in vitro, although one strain of gonococcus became more susceptible to streptomycin after it had acquired resistance to penicillin.¹²⁷ Organisms acquiring streptomycin resistance remain sensitive to sulfonamides.¹⁰⁷ 189

Resistance and Virulence

There was no loss of virulence with increase of resistance in vitro of meningococci.¹²⁷ Strains of tubercle bacilli becoming resistant in vitro and in vivo remained virulent for mice¹⁹³ and guinea pigs.¹⁰⁷ 195

Mechanism of Development of Resistance

The mechanism by which resistance to an antibacterial agent develops in a culture is still a matter for speculation. The possibilities that have been mentioned include natural selection from a heterogeneous population, modification of the individual cell by establishment of alternative internal mechanisms within the cell or by qualitative or quantitative modifications of existing mechanisms, particularly enzyme systems, and changes in some center

tion contained 500 to 1000 units per cubic centimeter.³⁷ Intradermal injection caused slight local reddening, whereas subcutaneous injection of some lots resulted in edema, hemorrhage and necrosis.³⁷ No serious local effects were noted after intramuscular injection in rabbits.^{37, 184} Thromboses did not result from intravenous injections.³⁷ Rabbits receiving 100 mg per kilogram of body weight intrapleurally showed areas of hemorrhage and fibrous adhesions.³⁷

The application of 1250 units of streptomycin to the cerebral cortex of cats and monkeys has caused convulsive manifestations in 30 per cent of the animals tested. These effects were less marked than those produced by comparable amounts of penicillin, as judged by clinical and electroencephalographic observations. The cisternal injection of 2500 units or more in monkeys produced signs of severe cerebellar dysfunction manifested by unsteadiness, ataxia and inability to stand up, accompanied by spontaneous nystagmus and tremor of the head.¹⁸⁵ Rabbits tolerated 10 mg of streptomycin per kilogram of body weight intracisternally in 0.5 cc of distilled water, but respiratory failure and death resulted from a similar injection of 20 mg.¹⁸⁶

Special Effects

Streptomycin exhibited a low toxicity for rabbit spleen in tissue culture,¹⁸⁷ whereas concentrations of 200 units per cubic centimeter were mildly inhibitory for fibroblasts and epithelial cells.¹⁸⁴ Toxicity for developing chick embryos is likewise low, as noted above.

Some of the toxic effects encountered in the experimental use of streptomycin, such as lipid infiltration of the kidneys and liver in monkeys and the vestibular difficulties in dogs and man, seem to be caused by streptomycin itself. At least two other toxic effects are due to impurities. One of these impurities is a histamine-like substance that produces a vasodepressor action and has probably been responsible for many of the undesirable immediate effects. This action may be removed by incubation with histaminase.^{37, 188} The same substance may also be responsible for the antidiuretic action noted with some batches.³⁷ A separate impurity, not yet identified, gives rise to the increased intravenous toxicity of some batches.³⁷

RESISTANCE TO STREPTOMYCIN

It was pointed out above that different strains of the same organism may vary considerably in their sensitivity to streptomycin. Strains of considerable resistance may occur among species of bacteria that are predominantly sensitive. Even within a given strain, there may be great differences in the sensitivity of individual cells.

Development of Resistance in Vitro

It was early shown that organisms could develop increased resistance to streptomycin. Waksman³⁹ was able to increase the resistance of a strain of *Pr. vulgaris* by growing it in sublethal concentrations of streptomycin. Resistance is usually increased in vitro by exposing bacteria to increasing amounts in fluid or solid mediums, the medium chosen being one that would normally support good growth of the particular organisms. Experiments have also been carried out with urine as a culture medium.¹¹¹ The resistance of a variety of bacteria has been increased in relatively short periods with the use of one or another of these methods. The development of resistance has not been found to be associated with the production by the organism of a streptomycin-inhibiting substance analogous to penicillinase.^{36, 61, 62}

The following bacteria have been found to develop resistance in vitro: staphylococci,^{61, 189, 190} *Str. faecalis*,¹¹¹ meningococci,¹²⁷ gonococci,¹²⁷ *Esch. coli*,^{111, 191} *A. aerogenes*,^{111, 191} *K. pneumoniae*,^{100, 191} species of *Shigella*,⁵⁹ paracolon bacilli,¹⁹¹ *Pr. vulgaris*,^{111, 191} *Ps. aeruginosa*,^{111, 191} *H. influenzae*,¹²⁰ and *Mycobacterium tuberculosis* (human^{107, 192} and avian¹⁰⁷ forms and a non-pathogenic strain of *Mycobacterium*¹⁰⁷). The rate of increase in resistance is generally expressed by the number of transfers needed to habituate the organism to growing uninhibited in some arbitrarily chosen concentration. Resistance may be acquired rapidly, particularly by *Ps. aeruginosa*, meningococci and gonococci. Other organisms require a greater number of transfers, but less than fifty usually suffice in the majority of those studied.^{127, 191} The development of in vitro resistance of tubercle bacilli to both streptomycin and sulfonamides was retarded when the organisms were exposed to both agents simultaneously.¹⁰⁷

Most workers have not studied increases in resistance to levels greater than 1000 units per cubic centimeter because of the amount of streptomycin required. When this has been done, however, resistance to over 50,000¹⁹¹ and even over 75,000¹²⁷ units per cubic centimeter was readily obtained. These values represent essentially the limit of workable concentrations. The rate of increase in resistance seemed to be more rapid on surface than in liquid mediums.¹⁹¹

Effect of Streptomycin on Infections Produced by Resistant Strains

Mice infected with lethal doses of strains of *Staph. aureus*,⁶¹ *Mycobacterium tuberculosis*,^{120, 193} *H. influenzae*,¹⁴ and meningococci¹²⁷ that had been made resistant were not protected by large doses of streptomycin. Mice infected with the parent streptomycin-sensitive strains of similar virulence were protected, usually by small doses. Infections produced by the streptomycin-resistant strains of *Staph. aureus* were favorably influenced by penicillin.⁶¹

6. Donovick, R., and Rake, G. Influence of certain substances on activity of streptomycin. I. Modifications in test medium. *Proc Soc Exper Biol & Med* 61:224-227 1946
7. Alexander H. E. Streptomycin in pediatrics. *J Pediatr* 29:192-198 1946.
8. Berkman S., Henry R. J., and Housewright, R. D. Factors influencing activity of streptomycin. Presented at Conference on Antibiotics Washington, D. C., January 31 and February 1 1947
9. Klein M., and Kimmelman, L. J. Role of spontaneous variants in acquisition of streptomycin resistance by *Shigella*. *J Bact* 52:471-479, 1946
10. Abraham E. P., and Duthie, E. S. Effect of pH of medium on activity of streptomycin and penicillin and other chemotherapeutic substances. *Lancet* 1:455-459 1946
11. Wolfinsky E., and Steenken W. Jr. Streptomycin and penicillin resistant staphylococci: influence of pH body fluids on streptomycin action. *Proc Soc Exper Biol & Med* 62:162-165 1946
12. Hall W. H., and Spink W. *In vitro* sensitivity of brucella to streptomycin: development of resistance during streptomycin treatment. *Proc Soc Exper Biol & Med* (in press)
13. Hobby G. L., Lenert F. and Hyman B. Factors influencing action of streptomycin *in vitro*. *J Bact* 51:606 1946 (Abstr.)
14. Hobby G. L., and Lenert T. F. Action of streptomycin *in vitro*. Presented at Conference on Antibiotics Washington, D. C., January 31 and February 1, 1947
15. Bugge C. W., Bronstein, B. Hirschfeld J. W. and Pilling M. A. Presence in normal serum of inhibiting substances against *Bacillus subtilis*. *Science* 103:363 1946
16. Peckman W. S. Subcutaneous vs intramuscular administration of penicillin. *J Lab & Clin Med* 31:1165-1169 1946
17. Levy G. B. Schwed P. and Sackett J. W. Polarographic analysis of streptomycin. *J Am Chem Soc* 68:328 1946
18. Smid J. V., Boxer G. E., and Jelinek V. C. Color reaction given by streptomycin. *Science* 104:486 1946
19. Zintel, H. A., and others. Studies on streptomycin in man. I. Absorption, distribution, excretion and toxicity. *Am J M Sc* 210:421-430 1945
20. Anderson D. G. and Jewell M. Absorption, excretion and toxicity of streptomycin in man. *Am J Med* 233:485-491 1945
21. Heilman, D. H. and others. Streptomycin absorption, diffusion, excretion and toxicity. *Am J M Sc* 210:576-584 1945
22. Bugge C. W., Pilling M. A., Bronstein B. and Hirschfeld J. W. Absorption, distribution and excretion of streptomycin in man. *J Clin Investigation* 25:94-102 1946
23. Adecock J. D., and Hettig R. A. Absorption, distribution and excretion of streptomycin. *Arch Int Med* 77:179-195 1946
24. Hirschfeld, J. W. and others. Streptomycin in treatment of surgical infections: report of experiences with its use. *Arch Surg* 52:357-401, 1946
25. Logan G. B., and Herrell W. E. Streptomycin in treatment of infectious meningitis of children. *Proc Staff Meet Mayo Clin* 21:393-400 1946
26. Stebbins R. B. Graessle O. E., and Robinson H. J. Studies on absorption and excretion of streptomycin in animals. *Proc Soc Exper Biol & Med* 60:68-72 1945
27. Rake, G., and Donovick, R. Use of mouse in studies on streptomycin. *Proc Soc Exper Biol & Med* 64:22-25 1947
28. Graham, B. E., Vander Brook, M. J. and Kuizenga M. H. Preliminary studies on absorption and excretion of streptomycin in dogs. *Science* 103:564 1946
29. Kolmer, J. A., Bondi A. Jr., Warner H. F. and Dietz C. Administration of streptomycin in peanut oil and beeswax and in solvex. *Science* 104:315-317 1946
30. Alexander H. E., Leidy, G. Rake G. and Donovick R. Hemophilus influenzae meningitis treated with streptomycin. *J A M A* 132:434-440 1946
31. Paine T. F., Murray R., Harris H. W. and Finland M. Streptomycin in treatment of certain gram negative bacillus infections of central nervous system. *Am J M Sc* (in press)
32. Harris, H. W., Murray R., Paine T. F., and Finland M. Streptomycin treatment of pulmonary infections: clinical and bacteriologic studies of six cases. *New Eng J Med* 236:611-622 1947
33. Robinson, H. J. Streptomycin and streptothricin: absorption, excretion and chemotherapeutic properties. *Ann New York Acad Sc* 48:119-142 1946
34. Remann H. A. Price A. H. and Elias W. F. Streptomycin for certain systemic infections and its effect on urinary and fecal flora. *Arch Int Med* 76:269-277 1945
35. Harris H. W. and others. Streptomycin treatment of urinary tract infections with special reference to use of alkali. *Am J Med* 2:229-250 1947
36. Zintel H. A., Wiley M. Nichols A. and Rhoads J. E. Use of streptomycin in surgical patients. *Surgery* 21:175-183 1947
37. Nelson W. E., Foregas J. and Kucera J. L. Alteration of distribution and excretion of streptomycin. *Proc Soc Exper Biol & Med* 64:20 1947
38. Murphy J. J., Ravdin R. G. and Zintel H. A. Use of streptomycin in experimental peritonitis. *Surgery* 20:445-451 1946
39. Zarlow J., Counsellor V. S. and Heilman F. R. Excretion and concentration of penicillin and streptomycin in abnormal human urinary tract. I. Gall bladder. *Surg Gynec & Obst* 84:16-20 1947
40. *Ibid.* Excretion and concentration of penicillin and streptomycin in abnormal human urinary tract. II. Hepatic bile. *Surg Gynec & Obst* 84:140-152 1947
41. Leonard I. H., and Nichols A. Intraocular penetration of streptomycin following systemic and local administration. *Arch Ophth* 35:33-38 1946
42. Woltz J. H. E. and Wiley M. M. Transmission of streptomycin from maternal blood to fetal circulation and amniotic fluid. *Proc Soc Exper Biol & Med* 60:105 1945
43. Denkelwater R., Cook M. A. and Tishler M. Effect of cysteine on streptomycin and streptothricin. *Science* 102:12 1945
44. Cavallito C. J. Relation of thiol structures to reaction with antibiotics. *J Biol Chem* 164:29-34 1946
45. Van Dolah, R. W. and Christenson G. L. Chemical inactivation of streptomycin. *Arch Biochem* 12:7-12 1947
46. Bondi A. Jr., Dietz C. C., and Spaulding E. H. Interference with antibacterial action of streptomycin by reducing agents. *Science* 103:399-401 1946
47. Rake G. and Donovick, R. Procedure for testing sterility of concentrated streptomycin solutions. *Proc Soc Exper Biol & Med* 62:31-33 1946
48. Waksman S. A. and Reilly, H. C. Bactericidal action of antibiotic substances. *J Infect Dis* 75:150-159 1944
49. Waksman, S. A., Reilly H. C., and Schatz, A. Strain specificity and production of antibiotic substances. V. Strain resistance of bacteria to antibiotic substances, especially streptomycin. *Proc Nat Acad Sc* 31:157-164 1945
50. Hamre D., Rake G. and Donovick R. Bactericidal action of streptomycin. *Proc Soc Exper Biol & Med* 62:25-31 1946
51. Strauss E. *In vitro* observations of mode of action of streptomycin. *Proc Soc Exper Biol & Med* 64:97-101 1947
52. Robinson H. J., Smith D. G., and Graessle O. E. Chemotherapeutic properties of streptomycin. *Proc Soc Exper Biol & Med* 57:226-231 1944
53. Reilly, H. C., Schatz A. and Waksman S. A. Antifungal properties of antibiotic substances. *J Bact* 49:585-594 1945
54. Welch H., Price C. W. and Randall W. A. Increase in fatality rate of *E. typhosa* for white mice by streptomycin. *J Am Pharm A (Scient Ed)* 35:155-158 1946
55. Chapman S. S., Downs C. M. and Kowal S. F. Studies on bacteriostatic and bactericidal action of streptomycin on *Bacterium tularensis*. *J Bact* 51:606 1946 (Abstr.)
56. Hamre D., Rake G. and Donovick R. Bactericidal action of streptomycin. *Federation Proc* (Part II) 5:247 1946
57. Middlebrook G. and Yegian D. Certain effects of streptomycin on mycobacteria *in vitro*. *Am Rev Tuberc* 54:553-558 1946
58. Neter E. Effects of penicillin, clavacin and streptomycin upon tetanus toxin. *J Infect Dis* 76:20-23 1945
59. Cohen S. S. Streptomycin and deoxynibonuclease in study of variations in properties of bacterial virus. *J Biol Chem* 166:393 1946
60. Bugge C. W., Bronstein B., Hirschfeld J. W. and Pilling M. A. *In vitro* action of streptomycin on bacteria. *J A M A* 130:64-67 1946
61. Knop C. Q. Experimental study of development of resistance to streptomycin by some bacteria commonly found in urinary infections. *Proc Staff Meet Mayo Clin* 21:273-276 1946
62. Live I., Sperling F. G. and Stubbs E. L. Effect of streptomycin on experimental brucellosis in guinea pigs. *Am J M Sc* 211:267-272 1946
63. Roessler W. G. and others. Studies with *Coccidioides immitis*. *J Infect Dis* 79:25-26 1946
64. Schatz, A. and Waksman S. A. Effect of streptomycin and other antibiotic substances upon *Mycobacterium tuberculosis* and related organisms. *Proc Soc Exper Biol & Med* 57:244-248 1944
65. Mortara F. and Saito M. T. Sensitivity of *Aspergillus fumigatus* to streptomycin *in vitro*. *J Gen Dis Inform* 27:152-154 1946
66. Mortara F. and Saito M. T. Sensitivity of *Hemophilus dysenteriae* to antibiotic and other substances *in vitro*. *Am J Syph Gonorr & Ven Dis* 30:352-360 1946
67. Murray R., Paine T. F., and Finland M. Unpublished data
68. Hewitt W. L. and Pittman M. Antibacterial action of penicillin, penicillin V, and streptomycin on *Hemophilus influenzae*. *Pub Health Rep* 61:768-778 1946
69. Birmingham J. R., Kaye R. and Smith M. H. D. Streptomycin in treatment of influenza meningitis. *J Pediatr* 29:1-13 1946
70. Alexander H. E. and Leidy G. Influence of streptomycin on type b *Hemophilus influenzae*. *Science* 104:101 1946
71. Hegarty C. P., Thiele E. and Verwey W. F. *In vitro* and *in vivo* activity of streptomycin against *Hemophilus artus*. *J Bact* 50:651-654 1945
72. Seabury J. H. and Arus D. *In vitro* susceptibility of *Histoplasma capsulatum* to therapeutic agents. *Proc Soc Exper Biol & Med* 61:15 1946
73. Heilman F. R. Streptomycin in treatment of experimental infections with micro-organisms of Friedlander group (Klebsiella). *Proc Staff Meet Mayo Clin* 20:33-39 1945
74. Youmans G. P. and Feldman W. H. Sensitivity of tubercle bacilli *in vitro* to streptomycin. *J Bact* 51:603 1946 (Abstr.)
75. Youmans G. P. Effect of streptomycin *in vitro* on *M. tuberculosis var. hominis*. *Quart Bull Northwestern Univ M School* 19:207-209 1945
76. Feldman W. H. Studies in chemotherapy of tuberculosis including use of streptomycin. *Tr & Stud, Coll Physicians Philadelphia* 14:81-97 1946
77. Miller C. P. and Bohnhoff M. Streptomycin resistance of gonococci and meningococci. *J A M A* 130:485-488 1946
78. Hornbrook J. W. Streptomycin in experimental plague. *Pub Health Rep* 61:535-538 1946
79. Heilman F. R. Streptomycin in treatment of experimental tularemia. *Proc Staff Meet Mayo Clin* 19:553-559 1944
80. Chapman S. S. and others. Studies on streptomycin therapy of experimental tularemia in white mice. *J Bact* 51:607 1946 (Abstr.)

of organization of the cell¹⁹⁹ Demerec²⁰⁰ has visualized two possible methods by which organisms may develop resistance to penicillin by the acquisition of this characteristic through contact with the agent and as an inherited character originating through mutation. His experiments and those of Luria²⁰¹ suggest that the latter is the more probable method.

Highly resistant variants have been found in each of six strains of *Shigella* not previously exposed to streptomycin by subjecting large numbers of bacteria (up to eight billion) to the action of various concentrations of the antibiotic.⁵⁹ The ratio of resistant variants to total organisms was estimated at from 1 500,000,000 to 1 16,000,000,000, depending on the strain. Furthermore, susceptible organisms produced resistant variants in the same proportion, even after a series of six consecutive single-colony selections of presumably susceptible cells. A few variants of *A. aerogenes* and *K. pneumoniae* that were resistant to over 50,000 units per cubic centimeter were found to develop from inoculums of several billion relatively sensitive organisms on agar plates containing streptomycin.¹⁹¹ The development of resistance to streptomycin, therefore, seems to be the result of the occurrence of resistant variants and subsequent selection by a high streptomycin concentration.

Washed cells of two strains of *Shigella* suspended in physiologic saline solution and exposed to streptomycin for seven days under varying conditions failed to show any increase in resistance to streptomycin.⁵⁹ The failure of *Esch. coli* in the resting state to develop resistance on exposure to streptomycin has also been demonstrated.¹⁰¹

(To be concluded)

REFERENCES

- Schatz A, Bugie E and Wakeman S A. Streptomycin, substance exhibiting antibiotic activity against gram positive and gram-negative bacteria. *Proc Soc Exper Biol & Med* 55:66-69 1944
- Wakeman S A and Schatz A. Streptomycin—origin nature and properties. *J Am Pharm A (Scient Ed)* 34:273-291 1945
- Wakeman S A, and Woodruff H B. Streptothricin, new selective bacteriostatic and bactericidal agent particularly active against gram negative bacteria. *Proc Soc Exper Biol & Med* 49:207-210 1942
- Wakeman, S A. Production and activity of streptothricin. *J Bact* 46:299-310 1943
- Idem. *Microbial Antagonisms and Antibiotic Substances* 350 pp. New York: Commonwealth Fund 1945
- Wakeman S A and Henriksen A T. Nomenclature and classification of actinomycetes. *J Bact* 46:337-341, 1943
- Whiffen, A J, Bohonos, N and Emerson R L. Production of anti-fungal antibiotic by *Streptomyces griseus*. *J Bact* 52:610 1946
- Leach B E, Ford J H and Whiffen, A J. Actedione antibiotic from *Streptomyces griseus*. *J Am Chem Soc* 69:474 1947
- Reynolds, D M, Schatz, A and Wakeman S A. Grisein new antibiotic produced by strain of *Streptomyces griseus*. *Proc Soc Exper Biol & Med* 64:50-54 1947
- Wakeman, S A, Schatz, A and Reilly H C. Metabolism and chemical nature of *Streptomyces griseus*. *J Bact* 51:753-759 1946
- Rake G, and Donovan R. Studies on nutritional requirements of *Streptomyces griseus* for formation of streptomycin. *J Bact* 52:223-226 1946
- Kuehl, F A, Jr, Peck R L, Walz, A, and Folkers K. Streptomycin antibiotics. I. Crystalline salts of streptomycin and streptothricin. *Science* 102:34 1945
- Vander Brook M J, Wick A N, De Vries W H, Harris R and Cartland G F. Extraction and purification of streptomycin, with note on streptothricin. *J Biol Chem* 165:463-468 1946
- Fried, J, and Wintersteiner O. Crystalline reneekates of streptothricin and streptomycin. *Science* 101:613-615 1945
- Peck, R L, and others. Streptomycin antibiotics. II. Crystalline streptomycin trihydrochloride—calcium chloride double salt. *J Am Chem Soc* 67:1866 1945
- Fried J, and Wintersteiner, O. Composition of streptomycin reneekate. *Science* 104:273, 1946
- Brink, N G, Kuehl, F A, Jr., and Folkers K. Streptomycin antibiotics. III. Degradation of streptomycin to streptobiosamine derivatives. *Science* 102:505 1945
- Fried, J, Boyack, G A, and Wintersteiner O. Streptomycin chemical nature of streptidine. *J Biol Chem* 162:391, 1946
- Peck R L and others. Streptomycin antibiotics. IV. Hydrolytic cleavage of streptomycin to streptidine. *J Am Chem Soc* 68:29-31 1946
- Carter, H E, and others. Degradation of streptomycin and structure of streptidine and streptamine. *Science* 103:53 1946
- Peck R L, and others. Streptomycin antibiotics. VII. Structure of streptidine. *J Am Chem Soc* 68:776-781, 1946
- Fried, J and Wintersteiner, O. Streptomycin. II. Reduction and oxidation products of streptomycin and of streptobiosamine. *J Am Chem Soc* 69:79-86 1947
- Schenck, J R and Spielman, M A. Formation of maltol by degradation of streptomycin. *J Am Chem Soc* 67:2276 1945
- Kuehl, F A, et al. Streptomycin antibiotics. V. N-methyl-glucosamine from streptomycin. *J Am Chem Soc* 68:556, 1946
- Fried, J, Walz D E, and Wintersteiner O. Streptomycin. III. 4-desoxy-l-erythrose (threose) phenylazone from streptobiosamine. *J Am Chem Soc* 68:2746, 1946
- Carter, H E, and others. Isolation and purification of streptomycin. *J Biol Chem* 160:337-342, 1945
- LePage, G A, and Campbell E. Preparation of streptomycin. *J Biol Chem* 162:163-171, 1945
- Peck, R L, Hoffhine C E, Jr and Folkers K. Streptomycin antibiotics. IX. Dihydrostreptomycin. *J Am Chem Soc* 68:1390 1946
- Bartz Q R, Controulis J, Crooks H M, Jr and Rebstock, M C. Dihydrostreptomycin. *J Am Chem Soc* 68:2163-2166 1946
- Donovick, R, and Rake, G. Studies on some biological aspects of dihydrostreptomycin. *J Bact* 53:205-211, 1946
- Pulaski E J. Streptomycin in surgical infections. II. Infections of genito-urinary tract. *Ann Surg* 124:392-401, 1946
- Regna, P P, Wasselle, L A., and Solomons, I A. Stability of streptomycin. *J Biol Chem* 165:631-638, 1946
- Oswald E J and Nielsen J K. Studies on stability of streptomycin in solution. *Science* 105:184, 1947
- Wakeman, S A, Bugie E and Schatz A. Isolation of antibiotic substances from soil micro-organisms with special reference to streptothricin and streptomycin. *Proc Staff Meet, Mayo Clin* 19:537-548, 1944
- Heilman, D H. Method for estimating concentration of streptomycin in body fluids. *Proc Staff Meet, Mayo Clin* 20:146-150, 1945
- Geiger, W B, Green, S R. and Wakeman, S A. Inactivation of streptomycin and its practical applications. *Proc Soc Exper Biol & Med* 61:187-192 1946
- Molitor, H, and others. Some toxicological and pharmacological properties of streptomycin. *J Pharmacol & Exper Therap* 86:151-173, 1946.
- Wakeman, S A. Standardization of streptomycin. *Science* 102:40, 1945
- Veldee, M V, Herwick R P, and Coghill, R D. Recommendations of International Conference on Penicillin. *Science* 101:42 1945
- Council on Pharmacy and Chemistry. New and Nonofficial Remedies. Streptomycin. *J A M A* 133:320, 1947
- Wakeman, S A and Reilly, H C. Agar streak method for assaying antibiotic substances. *Indust & Engin Chem (Analytical Ed)* 37:556-558, 1945
- Abraham E P, and others. Further observations on penicillin. *Lancet* 2:177-178 1941
- Stebbins, R B and Robinson H J. Method for determination of streptomycin in body fluids. *Proc Soc Exper Biol & Med* 59:255-257 1945
- Elias W F and Durso, J. Blood urine and fecal levels of streptomycin in treatment of human infectious of *E. typhosa*. *Science* 101:589-591 1945
- Reimann H A, Elias, W P, and Price, A H. Streptomycin for typhoid pharmacologic study. *J A M A* 128:175-180 1945
- Loo, Y H and others. Assay of streptomycin by paper-disc plate method. *J Bact* 50:701-709, 1945
- Kornegay G B, Forgacs, J and Henley, T F. Studies on streptomycin. II. Blood levels and urinary excretion in man and animals. *J Lab & Clin Med* 31:523-534 1946
- Rammekamp C H. Method for determining concentration of penicillin in body fluids and exudates. *Proc Soc Exper Biol & Med* 51:95-97 1942
- Donovick R, Haure D, Kavanagh, F and Rake G. Broth dilution method of assaying streptothricin and streptomycin. *J Bact* 50:623-628 1945
- Finland, M and others. Development of streptomycin resistance during treatment. *J A M A* 132:16-21 1946
- Altura Werber, E and Loewe, L. Method for routine determination of streptomycin levels in body fluids. *Proc Soc Exper Biol & Med* 63:277-280 1946
- Price, C W, Nielsen J K and Welch, H. Estimation of streptomycin in body fluids. *Science* 103:56 1946
- Pulaski, E J and Sprinz, H. Streptomycin in surgical infections. I. Laboratory studies. *Ann Surg* 125:194-202, 1947
- Osgood E E, and Graham, S M. Simple rapid method for assay of bactericidal and bacteriostatic agents. *Am J Clin Path* 17:95-107 1947
- Wallace, G J, Rhymer I, Gibson O and Shatzuck, M. Studies on mode of action of streptomycin. I. Effect of culture media. *Proc Soc Exper Biol & Med* 60:127 1945

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

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CASE 33191

PRESENTATION OF CASE

A seventy-eight-year-old widowed contractor was admitted to the hospital because of urinary frequency.

The patient had noted frequency, especially during cold weather, for over eight years. This had increased, until lately he had been voiding about every two hours during the day and once at night. He had had no dysuria, pyuria or hematuria. Following a recent cystoscopy the symptoms had become severer. On the morning of admission he was in a state of acute retention.

Physical examination showed slight enlargement of the heart. There was a soft, short systolic murmur at the apex and a loud rushing diastolic murmur that almost obscured the second sound. At the base there was a blowing systolic murmur, and the aortic second sound was not heard. The prostate was enlarged to twice the normal size. There was a moderate pitting edema of the ankles.

The blood pressure was 160 systolic, 85 diastolic. Examination of the blood disclosed a hemoglobin of 14.8 gm. The urine was red and gave a +++ test for albumin, and the sediment contained innumerable red cells. The nonprotein nitrogen was 30 mg per 100 cc. An x-ray film of the chest revealed a markedly enlarged heart, particularly in the region of the left ventricle. The aorta was tortuous and slightly dilated. An electrocardiogram revealed normal rhythm at a rate of 76 with considerable left-axis deviation, a low, diphasic T wave in Lead I and inverted T waves in Leads CF₁ and CF₂. A blood Hinton test was negative.

On the fourth hospital day a transurethral resection was performed. A moderate amount of bleeding was encountered. Near the end of the operation, the surgeon noticed a lack of return of irrigating fluid, and at the end of the operation it was noted that the abdomen was markedly distended. A suprapubic incision was made, and drainage of the peritoneal cavity and perivesical space was accomplished. Most of the fluid was anterior to the parietal peritoneum. At the end of the operation, the patient was in poor condition. Five per cent dextrose and water was given during the

operation, and immediately postoperatively two transfusions were administered. For the following week there was almost no urinary output. The nonprotein nitrogen by the third postoperative day had risen to 128 mg per 100 cc, the serum protein was 5 gm per 100 cc, and the chloride was 87 milliequiv and the carbon dioxide 20.3 milliequiv per liter. The suprapubic peritoneal drain was removed on the fifth postoperative day. The wound was in good condition, and peristalsis was noted. The nonprotein nitrogen, however, had risen to 185 mg per 100 cc, the chloride had fallen to 77 milliequiv and the carbon dioxide to 18.8 milliequiv per liter. On the following day the nonprotein nitrogen was 195 mg per 100 cc, the chloride was 79 milliequiv and the carbon dioxide 17.7 milliequiv per liter. On the sixth postoperative day a right nephrostomy and renal decapsulation were performed, and cloudy fluid was drained from the retroperitoneal region. Culture of this fluid revealed abundant colon bacilli and a few non-hemolytic streptococci. Twenty-four hours after decapsulation the nephrostomy tube began draining water-clear urine in increasing but small amounts and almost no urine was passed by way of the indwelling catheter in the bladder.

On the following day the patient suddenly became extremely short of breath and cyanotic. The neck veins were distended, the pulse was rapid, and rhonchi were heard in the chest. He was given aminophyllin, with dramatic improvement in breathing and color and some clearing of the chest signs. There were slight dullness and markedly diminished breath sounds at the right base, with some rales at both bases. On the next day the nonprotein nitrogen had reached 210 mg per 100 cc and the chloride 64 milliequiv and the carbon dioxide 22.2 milliequiv per liter. Two days later, the hemoglobin was 10 gm, the blood calcium was 7.2 mg, the phosphorus 14.7 mg, the nonprotein nitrogen 240 mg and the protein 6.2 gm per 100 cc and the chloride was 85 milliequiv, the carbon dioxide 19.4 milliequiv and the sodium 13.3 milliequiv per liter. On the next day a transfusion was administered. Twelve days after prostatectomy 450 cc of light, clear urine was collected from the nephrostomy tube, and the dressing was wet, but the nonprotein nitrogen had risen to 260 mg per 100 cc. On the following day the patient became extremely restless and expired.

DIFFERENTIAL DIAGNOSIS

DR. CHARLES BURNETT: The primary problem is to explain the renal failure in this patient, who, following transurethral resection, became anuric, developed uremia and died thirteen days after operation. I think that it is clear that he had prostatic obstruction of long standing, with urinary retention, and that he had benign hypertension and heart disease.

- 131 West, M G, Doll, E R, and Edwards P R Inhibition of *Salmonella* cultures by streptomycin *Proc Soc Exper Biol & Med* 60 363 1945
- 132 Priest W S and McGee, C J Streptomycin in treatment of subacute bacterial endocarditis report of three cases *J A M A* 132 124-126 1946
- 133 Loewe, L, Rosenblatt, P and Altire-Werber, E Refractory case of subacute bacterial endocarditis due to *Peillonella gasogenes* clinically arrested by combination of penicillin sodium paraaminosalicylate and heparin *Am Heart J* 32 327-338 1946
- 134 Reimann H A, Chang G C T, Chu L, Liu P Y, and Ou, Y Asiatic cholera clinical study and experimental therapy with streptomycin *Am J Trop Med* 26 631-647, 1946
- 135 Curran H R and Evans, F R Activity of streptomycin in relation to bacterial spores and preservation of milk *J Bact* 52 142 1946
- 136 Florman A L, Weiss A B and Council, F E Effect of large doses of streptomycin and influenza viruses on chick embryos *Proc Soc Exper Biol & Med* 61 16-18, 1946
- 137 Lowell F C, and Buckingham M Growth of influenza virus in eggs in presence of bacterial contamination and streptomycin *Proc Soc Exper Biol & Med* 62 228 231 1946
- 138 Kolmer J A and Rule A M Failure of penicillin and streptomycin in prophylaxis and treatment of experimental vaccinia in rabbits *Proc Soc Exper Biol & Med* 63 376 1946
- 139 Seeler A O, Malanga C, and Pierson J Effect of streptomycin on avian malaria *Proc Soc Exper Biol & Med* 59 291 1945
- 140 Bratton A C Jr Continuous intravenous chemotherapy of *Plasmodium lophocera* infection in ducks *J Pharmacol & Exper Therap* 85 103-110 1945
- 141 Williams L F and Plastridge, W N Use of antibiotic substances for freeing *Trichomonas fetus* from bacteria *J Bact* 51 127 1946 (Abstr)
- 142 Quisno R A, and Foter M J Use of streptomycin in purification of cultures of *Trichomonas vaginalis* *J Bact* 51 404 1946 (Abstr)
- 143 Herrold R D Indications for antibiotics (penicillin and streptomycin) in urinary tract infections *Illness M J* 90 216-221 1946
- 144 Kempe C H, Shaw E B and Silver H K Clinical applications of chick embryo cultures I Primary diagnosis of meningitis and study of spinal fluid in meningococcemia without meningitis II In vivo streptomycin sensitivity test *Am J Dis Child* 72 281 295, 1946
- 145 Seligman E, Barash L and Cohan S Q Streptomycin treatment of salmonella enteritis in infants *J Pediatr* 30 181 187, 1947
- 146 Jones D, Metzger H J, Schatz A and Wakeman S A Control of gram negative bacteria in experimental animals by streptomycin *Science* 100 103 105, 1944
- 147 Slanetz C A Control of salmonella infections in mice by streptomycin *Proc Soc Exper Biol & Med* 62 248 1946
- 148 Ordal, Z J and Meyer, E Effect of streptomycin on *Proteus* infections of chick embryo *J Bact* 52 67 70 1946
- 149 Wayson N E and McMahon M C Plague treatment of experimental animals with streptomycin, sulfadiazine and sulfapyrazine *J Lab & Clin Med* 31 323 332 1946
- 150 Bradford W L and Day E Therapeutic effect of streptomycin in experimental murine pertussis *Proc Soc Exper Biol & Med* 60 324 1945
- 151 Ryan F J and others Use of antibiotics vitamin analogues and other compounds in experimental gas gangrene *J Infect Dis* 78 223 231 1946
- 152 Muller E S and others Chemotherapy of experimental anthrax infections *J Immunol* 53 371 379, 1946
- 153 Klauder J V and Rule A M Penicillin and streptomycin in treatment of experimental *Erysipelothrix rhusiopathiae* infection of mice with observations on immunologic reaction to infection *J Invest Dermat* 7 329 336 1946
- 154 Powell, H M, Jamieson W A and Rice, R M Effectiveness of streptomycin in arthritis of rats *Proc Soc Exper Biol & Med* 62 8 1946
- 155 Feldman W H and Hinshaw H C Effects of streptomycin on experimental tuberculosis in guinea pigs preliminary report *Proc Staff Meet Mayo Clin* 19 593 599 1944
- 156 Feldman W H, Hinshaw H C, and Mann F C Streptomycin in experimental tuberculosis *Am Rev Tuberc* 52 269 298 1945
- 157 Rockwell G E Ineffectiveness of streptomycin on tubercular infections *J Bact* 51 607 1946 (Abstr)
- 158 Youmans, G P and McCarter J C Preliminary note on effect of streptomycin on experimental tuberculosis of white mice *Quart Bull Northwestern Univ M School* 19 210 1945
- 159 Idem Streptomycin in experimental tuberculosis its effect on tuberculous infections in mice produced by *M tuberculosis var hominis* *Am Rev Tuberc* 52 432-439 1945
- 160 Emmart E W Tuberculostatic action of streptomycin and streptomycin with special reference to action of streptomycin on choriomallantoic membrane of chick embryo *Pub Health Rep* 60 1415 1421, 1945
- 161 Smith M I and McClosky, W T Chemotherapeutic action of streptomycin and promin in experimental tuberculosis *Pub Health Rep* 60 1129 1138 1945
- 162 Smith M I, McClosky W T and Emmart E W Influence of streptomycin and promin on proliferation of tubercle bacilli in tissues of albino rat *Proc Soc Exper Biol & Med* 62 157 162 1946
- 163 Callomon, F T, Kolmer J A, Rule, A M, and Paul, A J Streptomycin and diosone in treatment of experimental tuberculosis in guinea pigs *Proc Soc Exper Biol & Med* 63 237-240 1946
- 164 Heilman, F R Streptomycin in treatment of experimental relapsing fever and leptospirosis icterohemorrhagica (Weill's disease) *Proc Staff Meet Mayo Clin* 20 169 176 1945
- 165 Dunham, W B, and Rake G Acitivity of streptomycin in experimental syphilis *Science* 103 363, 1946
- 166 Johnson, S A M, and Adcock, J D Treatment of experimental syphilis in rabbits with streptomycin *Proc Soc Exper Biol & Med* 62 109 111, 1946
- 167 Kolmer J A, Rule A M, and Paul A J Streptomycin in treatment of acute syphilitic orchitis of rabbits *Proc Soc Exper Biol & Med* 63 242, 1946
- 168 Fiske R A and Gruhitz, O M Effect of streptomycin on experimental syphilis infection of rabbits *Am J Syph, Gonorr & Ven Dis* 30 581 585, 1946
- 169 Meyer E and Ordal Z J Action of streptomycin and other antibiotic agents on *Blasomycetes dermatitidis* infections of chick embryo *J Infect Dis* 79 199 204 1946
- 170 Early R L and Morgan H R Studies on chemotherapy of viruses in psittacosis lymphogranuloma venereum group III Effect of certain chemotherapeutic agents on growth of psittacosis virus (6BC strain) in tissue cultures and eggs *J Immunol* 53 151 156 1946
- 171 Morgan H R Personal communication
- 172 Dunham, W B, and Rake G Action of chemotherapeutic agents on organism of granuloma inguinale *Federation Proc* (Part II) 5 246, 1946
- 173 Rake G and Hamre, D Activity of some antibiotics and sulfonamides in vitro and in vivo upon agents of lymphogranuloma venereum and feline pneumonitis *Federation Proc* (Part II) 5 253 1946
- 174 Morgan H R, Stevens D A and Snyder J C Effect of streptomycin on growth of Rickettsiae in eggs *Proc Soc Exper Biol & Med* 64 342 345 1947
- 175 Wall M J Isolation of virus of lymphogranuloma venereum from twenty-eight patients relative value of use of chick embryos and mice *J Immunol* 54 59-64 1946
- 176 Rose H M, Pearce E, and Molloy E Effect of penicillin and streptomycin on bacterial contamination of chick embryos inoculated with unfiltered sputums *Proc Soc Exper Biol & Med* 62 124-127 1946
- 177 Hodges J H Effect on chick embryo of simultaneous inoculation of stool streptomycin and penicillin *Science* 104 460 1946
- 178 Emerson G A, and Smith D G Induction of nutritional deficiency by oral administration of streptomycin *J Pharmacol & Exper Therap* 85 336-342 1945
- 179 Smith D G and Robinson H J Influence of streptomycin and streptomycin on intestinal flora of mice *J Bact* 50 613-621 1945
- 180 Brown, H A, and Hinshaw H C Toxic reaction of streptomycin on eighth nerve apparatus *Proc Staff Meet Mayo Clin* 21 347 352, 1946
- 181 Fowler E P Jr and Seligman, E Out complications of streptomycin therapy preliminary report *J A M A* 133 87 91 1947
- 182 Mushett C W and Martland H S Pathologic changes resulting from administration of streptomycin *Arch Path* 42 619-629 1946
- 183 Rutstein D D, Stebbins R B, Cathcart, R T and Harvey, R M Absorption and excretion of streptomycin in human chronic typhoid carriers *J Clin Investigation* 24 898-909, 1945
- 184 Howes E L Local chemotherapy of wounds tissue toxicity of certain antibacterial substances *Surg Gynec & Obst* 83 114 1946
- 185 Johnson H C, Walker, A E, Case T J and Kollros J Effects of antibiotic substances on central nervous system *Arch Neurol & Psychiat* 56 184-197 1946
- 186 Madigan, D G, Swift, P N, and Brownlee G Clinical and pharmacological aspects of toxicity of streptomycin *Lancet* 1 9 11 1947
- 187 Heilman, D H Cytotoxicity of streptomycin and streptomycin *Proc Soc Exper Biol & Med* 60 365 367 1945
- 188 Hewitt, W L and Curry, J J Pharmacodynamic effect in man of streptomycin containing histamine like factor *J Lab & Clin Med* 32 42-46 1947
- 189 Sullivan M, Stahl G L, and Birkeland J M Reciprocal sensitivities of *Staphylococcus aureus* to streptomycin streptomycin and penicillin *Science* 104 397 1946
- 190 Graessle O E and Frost B M Induced in vitro resistance of *Staphylococcus* to streptomycin and penicillin *Proc Soc Exper Biol & Med* 63 171-175 1946
- 191 Murray R, Kilham, L, Wilcox, C and Finland M Development of streptomycin resistance of gram negative bacilli in vitro and during treatment *Proc Soc Exper Biol & Med* 63 470-474 1946
- 192 Youmans G P, Williston L H, Feldman, W H and Hinshaw H C Increase in resistance of tubercle bacilli to streptomycin preliminary report *Proc Staff Meet Mayo Clin* 21 126 1946
- 193 Youmans G P and Williston E H Effect of streptomycin in experimental infections produced in mice with streptomycin resistant strains of *M tuberculosis var Hominis* *Proc Soc Exper Biol & Med* 63 131-134 1946
- 194 Petroff, B P and Lucas, F V Streptomycin in urinary infections *Ann Surg* 123 808 818, 1946
- 195 Gardner A D Microscopical effect of penicillin on spores and vegetative cells of bacilli *Lancet* 1 658, 1945
- 196 Spink, W W, Ferris V and Vivino, J J Antibacterial effect of whole blood upon strains of staphylococci sensitive and resistant to penicillin *Proc Soc Exper Biol & Med* 55 210-213 1944
- 197 Rake, G, McKee C M, Hamre D M and Houck C L Studies on penicillin II Observations on therapeutic activity and toxicity *J Immunol* 48 271-289 1944
- 198 Karlson A G, Feldman W H, and Hinshaw, H C Persistence of resistance of tubercle bacilli to streptomycin during passage through guinea pigs *Proc Soc Exper Biol & Med* 64 6 1947
- 199 Davies, D S, Hinshelwood C N and Pryce, J M Studies in mechanism of bacterial adaptation *Tr Faraday Soc* 40 397-419, 1944
- 200 Demerec M Production of staphylococcus strains resistant to various concentrations of penicillin *Proc Nat Acad Sc* 31 16-24 1945
- 201 Luria S E Test for penicillin sensitivity and resistance in staphylococcus *Proc Soc Exper Biol & Med* 61 46-51 1946

I suppose that one must also consider a benign nephrosclerosis, which was probably present to some extent, and it seems conceivable that acute renal insufficiency developed following the insult of operation, with nothing more demonstrable at autopsy. The patient may have had pyelonephritis and old hydronephrosis secondary to long-standing prostatic obstruction. The third possibility is the condition of so-called "reflex anuria," which occurs following urologic procedures. The anuria is presumably neurogenic in origin, and at autopsy no lesion can be demonstrated. I had not considered either bilateral cortical necrosis or periarteritis nodosa in this case, but they are, I suppose, possibilities.

I believe that the patient had hemoglobinuric nephrosis, in addition to uremia, hypertensive heart disease, calcareous aortic stenosis, some congestive heart failure, possibly some peritonitis and probably retroperitoneal infection.

DR. TRACY B. MALLORY: Dr. Smith, will you tell us your impression of the case?

DR. SMITH: The over-all impression is a sad one. This case began to go wrong when the spinal anesthetic did not work. After resection was started, the patient had pain, which I did not think at that time was due to extravasation of the urine, since I had hardly begun to resect. He was given inhalation anesthesia, and I went ahead with the resection. If he had not been under general anesthesia we would undoubtedly have noticed the leakage of fluid sooner, because these patients under spinal anesthesia are aware of pain when the fluid extravasates around the bladder. I thought that the point of leakage of the fluid was from the roof of the urethra, and when the operation was concluded and the patient lay flat on the table, it was seen that he had a marked swelling of the suprapubic region, so that we prepared for an abdominal operation as soon as possible.

As soon as the perivesical space was entered there was the escape of much slightly blood-stained fluid, which seemed to come largely from the perivesical space and more from the right side than the left. The peritoneum was opened purposely because the symptoms at the conclusion of the resection, when the patient quickly came out of general anesthesia, suggested that he had some intraperitoneal fluid. A small amount of clear fluid was obtained from the peritoneum, whereas the fluid from the perivesical space was bloody. Therefore, it did not seem likely that the rupture had extended into or involved the peritoneal portion of the bladder. A small drain was placed in the peritoneum, however. The bladder was opened, and a hasty exploration of the dome of the bladder revealed no rupture. The bladder was drained by a suprapubic tube.

It is surprising that although the heart seems to have been seriously damaged it took a terrific beating and got him through twelve days of the

hardest kind of going without failure. The case was handled carefully from the chemical point of view, Dr. Woodruff, the resident, followed the general rules of treatment in these cases that were laid down by Dr. George W. Thorn* in an admirable lecture that he gave before the Clinical Association of Genitourinary Surgeons. But it had become evident that the nonprotein nitrogen was going up steadily and rapidly, and the patient was still not excreting fluid. The experience that I had had with a few cases of anuria in the past indicated that decapsulation was certainly worth doing. The decapsulation and nephrostomy took about twenty minutes. The patient was much better the next morning, although he did not excrete fluid. He began to drain fluid two days after operation, but although 450 cc. of urine is a large enough output to enable a patient to get along without uremia if the urine is the product of a sufficient kidney, this was the product of an insufficient kidney with nephrosis of the lower nephrons. Nothing but water was being passed through the kidney. I suppose that if we could have kept him alive for another week or ten days the kidney tubular epithelium might have recovered enough so that he could have lived.

CLINICAL DIAGNOSES

Obstructing prostate
Hemoglobinuric nephrosis
Uremia

DR. BURNETT'S DIAGNOSES

Hemoglobinuric nephrosis
Uremia
Hypertensive heart disease
Calcareous aortic stenosis

ANATOMICAL DIAGNOSES

Hemoglobinuric nephrosis
Operative wounds: transurethral prostatectomy, drainage of perivesical space, and decapsulation of kidney
Prostatic hyperplasia
Endocarditis, chronic rheumatic, of aortic valve, with stenosis
Hypertrophy of heart
Arteriosclerosis generalized, moderate

PATHOLOGICAL DISCUSSION

DR. MALLORY: As Dr. Smith has said, a biopsy of one kidney was done at the time of decapsulation. Characteristic precipitated-hemoglobin casts were observed in the distal convoluted tubules. The biopsy, of course, had to be limited to the surface of the kidney and showed only the cortex. The major lesion in these cases is seen in the pyramids.

At autopsy we found evidence of a full-blown lesion—a great many pigment casts throughout the lower segments of the nephron, degeneration of the epithelium of Henle's loops and interstitial in-

May we see the x-ray films? Is there any evidence of left auricular enlargement?

DR STANLEY M WYMAN In the lateral view the retrocardiac space is not obliterated, and there is prominence in the region of the left ventricle. The concavity of the auricle is maintained at this point.

DR BURNETT How about the aorta?

DR WYMAN It is tortuous, but I do not believe that it is dilated. The transverse diameter seems to be within normal limits for a person of this age.

DR BURNETT Is there any evidence of congestive failure?

DR WYMAN I do not believe so.

DR BURNETT I believe that the cardiac lesion was caused by hypertensive heart disease and calcareous aortic stenosis and that the mitral murmur heard at the apex was due to hypertrophy and dilatation of the left ventricle. The electrocardiogram is also consistent with this diagnosis. There was some evidence of congestive failure in that pitting edema of the legs was observed. The laboratory data on admission showed proteinuria and hematuria and a compensated renal function, at least so far as the nonprotein nitrogen was concerned. Beyond that we are not given any data that tell what the renal reserve was.

I should like to ask a few questions. What was the nature of the fluid used in the irrigating solution? Was any evidence of hemoglobinuria, hemoglobinemia or icterus noted at any time postoperatively? Were sulfonamides administered at any time?

DR GEORGE G SMITH The fluid used was sterile tap water. The patient had not been given any sulfonamides except 1 gm of sulfadiazine after I cystoscoped him in my office. He had no icterus. It is unfortunate that we do not know about hemoglobinemia because Dr Woodruff has been checking that carefully on all transurethral prostatectomies, with interesting results. In this particular case he had the syringe ready, but in our haste to start the operation, he did not take the blood. Thus, in the one case in which we should particularly have liked to have a reading, no observation was made.

DR BURNETT From the description of the operation we may assume that a perforation of the bladder or the bladder neck had occurred. We are told that a considerable amount of bleeding was encountered and that the patient was in poor condition at the end of operation. Hence, he must have had at least some degree of shock, which I believe is the first factor that contributed to the fatal outcome.

Sterile tap water was used in the transurethral resection. It has recently been demonstrated by a number of workers that in this procedure a large number of veins are exposed in the prostatic bed, allowing ready access of the water to the veins and amounting to intravenous infusion of water, with the production of hemoglobinemia and renal failure.

Dr Joseph Ross¹ studied 23 cases recently, 15 of which developed hemoglobinemia, and in 6 the hemoglobinemia was of sufficient degree to produce hemoglobinuria. Two patients died, one of shock and the other of renal failure with a characteristic renal lesion. In this study the pressure of water used for irrigation was 100 mm. It is known that the pressure in the pelvic veins is 0-5 mm, and, indeed, in some cases it may be negative, so that it is not too surprising that intravascular hemolysis and hemoglobinemia result. This is a second factor that I believe to have contributed to the fatal outcome in the case under discussion.

The third factor is that two transfusions were given at the end of operation. We are not told whether a subsequent attempt was made to check the donors for the presence of incompatibility, but intravascular hemolysis of donor cells is always a possibility when a transfusion is given. Sulfonamides seem rather well excluded.

Hence, there were three factors capable of producing the hemoglobinuric or lower-nephron nephrosis that I believe was present in this case, and any one of these alone may produce it. Wounded battle casualties in severe shock and without any marked degree of pigment destruction have been shown to develop the lesion. The cause is thought to be partly renal ischemia, which is known to occur during shock and to persist for some time after recovery from shock. Hemolysis of one's own hemoglobin is known to produce the lesion if the hemolysis is of sufficient degree. Hemolysis of donor cells following transfusion of incompatible blood is too well known to require discussion.

The course in the case under discussion is compatible with such a diagnosis, as it is with any case of acute renal insufficiency. The progressive, severe azotemia, hypochloremia, acidosis, hypocalcemia, hyperphosphatemia and hyponatremia have all been seen and described in this syndrome. The episode on the eighth day may have represented pulmonary edema. In this particular type of acute renal insufficiency it has been demonstrated that the plasma volume is increased, — that is, that there is a true hydemia, — and I suspect that such an increase was present. The hypochloremia, as well as the fact that this man had a reduced cardiac reserve, readily explains the occurrence of acute pulmonary edema. Other possibilities are pulmonary infarction and atelectasis in the right lower lobe, as the signs suggested. The hemoglobin of 10 gm on the tenth day as compared to 15 gm on admission is confirmatory evidence of blood loss and possibly of a previous hemolysis.

The effect of decapsulation of the kidney is interesting. It appeared to increase the output of urine, especially on the side where it was done, and suggests that this procedure should be put to a fresh test in such cases.

malignant tumor of the esophagus, probably an epidermoid carcinoma

DR CHESTER M JONES Is the cardia of the stomach perfectly intact?

DR WYMAN I believe that the extreme distal esophagus and the cardia are normal

DR JONES In other words it appears that the tumor did not originate in the stomach, progressing up the esophagus. If it was carcinoma, I should be more inclined to call it an adenocarcinoma

DR TRACY B MALLORY On what basis? Because of its polypoid rather than constrictive growth?

DR JONES Yes

DR MCKITTRICK That is a pertinent suggestion and should have been considered in the diagnosis

CLINICAL DIAGNOSIS

Carcinoma of esophagus

DR MCKITTRICK'S DIAGNOSIS

Malignant tumor of esophagus, probably epidermoid carcinoma

ANATOMICAL DIAGNOSIS

Adenoacanthoma of cardia of stomach

PATHOLOGICAL DISCUSSION

DR SWEET This was a polypoid type of tumor, which is associated with the adenocarcinoma group, and it was one of the group of cases in which the cardia was actually 4 or 5 cm above the diaphragm. What looks like esophagus below the lesion was really stomach, so that this was a carcinoma of the cardia entirely above the diaphragm

DR MALLORY The specimen that Dr Sweet resected consisted of the lower part of the esophagus and the upper 7 cm of the stomach. A cancer was found centered at the cardiac orifice and extending in both directions, up into the esophagus and down into the cardia of the stomach. It was an adenocarcinoma, which in a few areas showed foci of squamous-cell formation and therefore falls in the group of tumors with both adenocarcinoma and squamous-cell carcinoma that are called adenoacanthomas. I do not believe that it is possible to be dogmatic about whether the origin was on the esophageal or the gastric side of the cardia, although adenoacanthomas are rare in the stomach and occasionally seen in the esophagus

inflammation I could distinguish no difference between the kidney that had been decapsulated and its mate. The proximal convoluted tubules and glomeruli, as usual, were normal except for a mild degree of dilatation. The lesion was, of course, indistinguishable from that which follows a transfusion reaction.

Checking back over cases of transurethral resection done in this hospital during the last seven or eight years, Dr. Firminger has found 5 similar cases. There have been none in patients on whom suprapubic or perineal prostatectomy has been performed.

The heart was moderately hypertrophied, weighing 490 gm., and the aortic valve had enough interadherence of the commissures to have produced slight stenosis. The coronary arteries showed only slight atheroma. The lungs were moderately edematous, as had been expected.

REFERENCES

1. Ross, J. Personal communication.
2. Thorn, G. W. Unpublished data.

CASE 33192

PRESENTATION OF CASE

A sixty-four-year-old postmaster entered the hospital because of postprandial distress and regurgitation.

Two months before admission, following a drink of whisky, the patient had experienced the first episode of distress in the lower middle portion of the chest anteriorly, followed by regurgitation of some mucus. A short time later, the same thing happened after a swallow of ginger ale. During the next two weeks several similar episodes occurred, in the intervening periods he could swallow food and fluids without trouble. Six weeks before admission substernal distress and regurgitation of clear mucus began to follow swallowing of solids as well as fluids. On one occasion, while eating a tough piece of steak, he felt a sensation "as though a pineapple were being forced through an ulcer." He had reduced his diet, and in the two months he had lost 15 pounds.

Physical examination was essentially negative except for bilateral saphenous varicosities.

The temperature, pulse and respirations were normal, as was the blood pressure.

Routine examinations of the blood and urine were negative, and the total protein, nonprotein nitrogen, sugar and prothrombin time were normal, as was an electrocardiogram. A gastrointestinal series demonstrated a lobulated ulcerated tumor mass, measuring approximately 11 cm. in length, that involved the lower end of the esophagus and arose from its right posterior wall. It produced only slight obstruction to the flow of barium. The esophagus immediately above the diaphragm ap-

peared free of tumor. The stomach showed no evidence of pathologic change.

On the fourth and eleventh hospital days blood Hinton tests were reported positive.

An operation was performed on the twelfth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. JOHN B. MCKITTRICK: In this patient with symptoms of two months' duration there had apparently been no history of previous trouble. The symptoms were characteristic of esophageal disease. I have the impression from the record that the symptoms were intermittent and that the inability to pass food down the esophagus was not steadily progressive. One fleetingly thinks of esophageal spasm or cardiospasm with such a history, but as a rule, cardiospasm is of longer duration, rarely appearing primarily in a sixty-four-year-old man.

The physical examination does not help a great deal, nor do the other studies that were done in the hospital prior to operation. The patient had lost considerable weight — 15 pounds — in two months on a starvation diet. The record does not specify what the diet was, but I assume that he had confined himself to food that he could swallow easily and that this was quite limited. Apparently, at that point, he had been eating solid food rather than liquid. In contradistinction to carcinoma, it might be mentioned that patients with esophageal spasm often swallow solid food better than liquid. Is that correct, Dr. Sweet?

DR. RICHARD H. SWEET: I believe so, the symptoms are intermittent, at any rate.

DR. MCKITTRICK: As I read the record I was puzzled by the description of the x-ray examination and was not able to make a diagnosis. "A lobulated ulcerated tumor mass" — an unusual description — is mentioned. I suppose that a malignant tumor of the esophagus could be so described. I am interested to know whether this tumor showed evidence of infiltration in the wall of the esophagus or of pedunculation. Can infiltration of the wall of the esophagus be ruled out?

DR. STANLEY M. WYMAN: Not without fluoroscopy. On the film, this must be what is described as the lobulated mass — large confluent masses of tissue obliterating the normal mucosal pattern. The ulcer that is spoken of is probably this shadow.

DR. MCKITTRICK: It is a sessile, ulcerated, lobulated tumor. I think that the only diagnosis that I can make is a malignant tumor of the esophagus. Tumors of this size can develop in the course of the short history that this patient gave. Carcinoma of the esophagus with few symptoms referable to the esophagus does occur. It is conceivable that tumors more obvious than this are less symptomatic. The two positive blood Hinton tests are interesting, but I do not believe that the x-ray picture is characteristic of syphilis of the esophagus. My diagnosis is

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THE FULMINANT FORM OF EPIDEMIC HEPATITIS

Lucke and Mallory¹ have recently described the clinical and anatomic findings in a group of fatal cases of acute epidemic hepatitis that may represent an entirely new form of this disease which they termed 'fulminant'. Epidemic hepatitis attained pandemic proportions during the war, it occurred in many parts of the world and probably in the armies of most, if not all, of the belligerent nations. In 1944 Lucke² described the pathology of this disease in 125 cases that were observed in the Army of the United States in 1942. During the period between August, 1943 and April, 1945 another series, consisting of 196 fatal cases, was accumulated at the Army Institute of Pathology. More than half the latter cases were of the acute form and were of intense severity, terminating fatally in less than ten days. By contrast, not a single equally fulminant case was encountered in the previous series, and this type of case has rarely been noted in other epidemics that have been reported. The usual duration of the fatal disease in Lucke's first series was from four to six weeks; in other words, the course of the fatal hepatitis was predominantly subacute.

This divergence in the duration of the fatal illness reflects the striking difference in the pertinent pathologic changes. Thus, in the fulminant form, the parenchyma of the liver is destroyed completely and uniformly, and this destructive process is accompanied by an intense inflammatory reaction. In the subacute form and in a quarter of the second series of cases, the destruction of the liver was incomplete; the involvement was characteristically

not uniform, regenerative hyperplasia of the surviving parenchyma led to the production of much new liver tissue and the inflammation was less pronounced.

The epidemiology of the cases also differed significantly. Most of the cases of hepatitis that occurred in 1942 followed the administration of yellow fever vaccine containing human serum. In the more recent series such vaccination had not been used but nearly half the patients had sustained combat injuries. Since most of the seriously wounded patients customarily received transfusions of whole blood, serum or plasma, it can be assumed that a high proportion of the wounded in the latter series were treated in this manner. It was not known, however, in how many cases the causal agent of hepatitis was introduced by therapeutic procedures, especially since large epidemics of hepatitis were prevalent in several of the theaters of war. The assumption that the cases among the wounded were examples of so-called "homologous serum hepatitis" seems justified largely by the relatively long interval between the time of the wound, and presumably of the first transfusion, and the time of onset of the clinical manifestation of the disease. About half the cases, which occurred in nonwounded persons, represented both the epidemic and the endemic variants of naturally occurring hepatitis. Lucke and Mallory's study is largely based on 94 fulminant cases in which the clinical duration did not exceed nine days but they also studied 39 additional cases that had a duration of from ten to nineteen days.

On the basis of epidemiology, 29 of the cases were classed as endemic and 72 as epidemic variants of spontaneous hepatitis and 77 cases were presumed to be homologous serum hepatitis following trauma and transfusions of blood or blood derivatives. A careful analysis showed that the epidemiologic type did not in any way determine either the clinical form or the pathological picture of the hepatitis, or whether the case was fulminant or subacute. There was no information whether the mortality rates were the same or different in the epidemiologic variants. The average mortality during the period covered by the study was 0.3 per cent. Serum hepatitis, however, tended to run a considerably shorter course than the naturally occurring disease.

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

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MATERIAL should be received not later than noon on Thursday three weeks before date of publication

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COMMUNICATIONS should be addressed to the *New England Journal of Medicine* 8 Fenway Boston 15 Massachusetts

COMING ANNUAL MEETING

THE one hundred and sixty-sixth anniversary of the Massachusetts Medical Society will be held at the Hotel Statler, Boston, on May 20, 21 and 22, and the program of the meeting appears elsewhere in this issue of the *Journal*

Owing to the fact that the program covers three full days, the meeting of the supervising censors and the annual meeting of the Council will be held in the late afternoon and early evening, respectively, on May 19

The first general session will begin at 9:05 a m on May 20, and four papers will comprise a symposium on industrial medicine. The annual meeting of the Society will be called to order at 11:00 a m and will be followed by the annual oration, "Medical Care in Our Free Society," by Dr Leland S McKittrick,

and by the annual luncheon. The second general session will begin at 2:00 p m and will be devoted to a symposium on the distribution of medical care for the people of Massachusetts. The speakers are Drs Elmer S Bagnall, Charles F Havden and Winthrop Adams and Messrs Reginald F Cahalane and Jarvis Hunt. The topics to be discussed include the attitude of the Massachusetts Medical Society, Blue Cross and Blue Shield, veterans' care and the industrial point of view. That evening, at 8:00, Dr William Dock, of Brooklyn, New York, will deliver the Shattuck Lecture, his title being "Clinical Significance of Circulatory Peculiarities of Some of the Vital Organs."

The third general session will open at 9:00 a m on May 21. The program lists seven papers on timely topics of general interest, such as infectious diarrhea of the newborn and the uses and abuses of chemotherapy. Four section meetings and luncheons are scheduled for the noon hour, and the fourth general session, which begins at 2:00 p m will comprise a symposium on bronchiectasis, consisting of five papers presenting the views of the pathologist, roentgenologist, internist, anesthetist and surgeon. A cocktail party will be held from 5:00 to 7:00, followed by the annual dinner, at which the guest speaker will be Dr Harrison H Shoulders, president of the American Medical Association.

The fifth and sixth general sessions will begin at 9:00 a m and 2:00 p m, respectively, on May 22. Fourteen talks on a miscellaneous group of topics are scheduled, and at noon four section meetings and luncheons will be held.

Although it has been necessary to eliminate the continuous motion-picture program and to cut down on the scientific exhibit owing to lack of space, the technical exhibit will be approximately as large as in previous years. Improvements in diagnostic aids and new therapeutic agents continue to appear at an amazingly rapid rate, and the technical exhibit offers an excellent opportunity for those who attend the meeting to become up to date.

The program for the wives of members includes a reception and tea at the Women's City Club, Boston, on the afternoon of May 20 and luncheon at The Country Club, Brookline, on the following day.

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Clinically, the fulminant form of hepatitis was characterized by its abrupt onset and by its severity. It was usually ushered in by one of two syndromes—an "infectious type," in which the disease began with fever, chilliness, shaking chills, malaise, generalized aching and pains in the joints, back and eyes, with gastrointestinal symptoms usually following in a day or so but rarely dominating the picture, or a "gastrointestinal type," with anorexia, nausea and epigastric discomfort as the presenting symptoms. These two types were about equally frequent and often occurred side by side during various epidemics. In the fulminant cases, the initial symptoms sometimes merged with those of the terminal stage, but the subsequent clinical manifestations bore no relation to the prodromal symptoms.

The temperature ranged from 95 to 104° F., with an average of 102°, and usually declined with the onset of jaundice. There was generally a terminal sharp rise in temperature coincident with the onset of profound cerebral disturbances. In contrast to the deep jaundice commonly observed in the subacute form, the jaundice in fulminant hepatitis was often mild, and several anicteric cases were observed. Moderate degrees of nitrogen retention and lowered blood sugar levels were among the noteworthy laboratory findings.

The pathologic lesions, other than those in the liver, were relatively slight. As previously mentioned, the changes in the liver were characterized by an extreme and often complete destruction of the hepatic cells and a marked inflammatory reaction, the involvement usually being uniform throughout the liver. The gross appearance gave no indication either of the extent of parenchymatous destruction or of the degree of inflammatory infiltration. The organ was usually flaccid and moderately shrunken, and the capsule was smooth or finely wrinkled. The cut surface generally presented an exaggerated "nutmeg" pattern, although sometimes it resembled that of an acutely congested spleen. Microscopically, the destructive

process was limited to the liver cells. Practically all the parenchymal cells were necrotic and had undergone lysis, and the resultant debris had already been removed at the time of death. The inflammatory cells consisted of mononuclear forms—reticuloendothelial derivatives, plasma cells and lymphocytes. Regenerative hyperplasia of the parenchyma was minimal and was confined to the biliary rather than to the hepatic epithelium. In most cases the pathologic changes in the liver were obviously older than the clinical history suggested, but sometimes the reverse was true.

The kidneys in the majority of cases were the site of fat storage, especially within the cells of the proximal convoluted tubules. There were no significant degenerative changes, and the findings were considered to be the result of the sudden liberation of large amounts of fat from the destroyed liver cells. There was no correlation between the degree of fat storage and the nitrogen retention. The so-called "hepatorenal syndrome," as usually defined, was not observed. Although marked nervous disturbances were noted clinically in the terminal stages, the histologic changes in the brain were usually slight, consisting of a mild and non-specific encephalopathy. Ascites was present in approximately a fourth of the cases of fulminant hepatitis, and its production was thought to be the result of acute venous stasis in the liver. The incidence of ascites and its extent, however, seemed to be directly proportional to the duration of the disease and were not related to the weight of the liver.

The factors responsible for the appearance of this fulminant form of hepatitis were difficult to assess. It was suggested that a number of more or less interrelated host factors, such as fatigue, trauma and nutritional disturbances, played a dominant role, rather than any specific property of the strain or the amount of the infectious agent.

REFERENCES

1. Lucké, B. and Mallory, T. Fulminant form of epidemic hepatitis. *Am. J. Path.* 22: 867-945, 1946.
2. Lucké, B. Pathology of fatal epidemic hepatitis. *Am. J. Path.* 20: 471-527, 1944.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

NEW DIRECTOR

Nicholas J. Fiumara, M.D. health officer of the Berkshire District of the State Department of Public Health, has been promoted to director of the Division of Venereal Diseases, pending qualification by the Division of Civil Service.

Dr. Fiumara succeeds Dr. George E. Perkins, of Belmont who died suddenly from injuries sustained in an automobile accident.

A former lieutenant in the Navy Medical Reserve Corps, Dr. Fiumara served with the Navy from June 1945 to July 1946. He held the successive posts of medical officer aboard the *USS Monomoy*, venereal-disease control officer in the Caribbean Theater and commanding officer of Epidemiology Unit 22, which saw service on the West Coast.

Since his detachment from the Navy last year, Dr. Fiumara has been attending the Harvard School of Public Health, from which it is expected he will receive the degree of Master of Public Health in June.

He is a member of the Massachusetts Medical Society, American Public Health Association and Massachusetts Public Health Association and a fellow of the American Medical Association.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR MARCH, 1947

DISEASES	RESUME		
	MARCH 1947	MARCH 1946	SEVEN YEAR MEDIAN
Chicken pox	3	1	2*
Diphtheria	054	191	1471
Dysentery	72	19	16
Dysentery bacillary	796	955	7
German measles	0	14	4
Scarlet fever	112	680	316
Gonorrhea	295	424	327
Gonorrhea inguinalis	0	1	1*
Lymphogranuloma venereum	0	2	2
Malaria	8	63	3
Measles	1794	701	5126
Meningitis meningococcal	2	12	21
Meningitis Pfeiffer bacillus	0	4	4
Meningitis pneumococcal	1	0	0*
Meningitis staphylococcal	0	0	0*
Meningitis streptococcal	0	0	1*
Meningitis other forms	1	1	1*
Meningitis, undetermined	0	2	4*
Polio	1178	851	1349
Pneumonia, lobar	17	24	37
Pneumonia, bronchopneumonia	17	24	37
Scarlet fever	1	2	1
Cytitis	10	542	145
Tuberculosis pulmonary	564	453	479
Tuberculosis, other forms	17	248	248
Typhoid fever	14	2	20
Undulant fever	1	1	2
Whooping cough	64	592	555
*Three-year median			
*Five-year median			

COMMENTS
Diphtheria once again was the leading disease of the month. The number of cases reported has essentially the same ratio to those of 1946 and the seven-year median as that reported in February, however, the number of cases shows an increase of 18 cases over the number of cases reported in February.

Chicken pox was still increased as compared with the number of cases reported in March 1946, but the excess was not so marked, being approximately three times the number of

cases reported in March, 1946, and three times the seven-year median.

Measles and German measles both showed a marked drop compared to the number of cases reported in March, 1946, and to the seven-year median. German measles, in particular being approximately one sixth the number of cases reported in March, 1946 and one third the seven-year median.

Diseases above the seven-year median were dog bite, bacillary dysentery, poliomyelitis, salmonellosis and undulant fever.

Scarlet fever is at the lowest level since 1918.

Below the seven-year median are gonorrhea, meningitis, lobar pneumonia, syphilis, typhoid fever and whooping cough.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Abington, 1, Belmont, 1, Boston, 30, Cambridge, 1, Chelsea, 3, Chicopee, 5, Easthampton, 2, Everett, 1, Lowell, 1, Lynn, 1, Medford, 1, New Bedford, 4, Newbury, 1, Newton, 1, Norton, 1, Peabody, 1, Reading, 2, Revere, 5, Saugus, 1, Somerville, 3, Southwick, 1, Wellesley, 1, West Newbury, 1, West Springfield, 1, Winchester, 1, Winthrop, 1, total, 72.

Dysentery amebic was reported from Boston, 1, Cambridge, 1, Quincy, 1, total, 3.

Dysentery bacillary was reported from Melrose, 3, Worcester (State Hospital), 6, total, 9.

Encephalitis infectious was reported from Middleboro, 1, New Bedford, 1, total, 2.

Hookworm was reported from Lowell, 1, total, 1.

Lymphocytic chorion meningitis was reported from Weymouth, 1, total, 1.

Malaria was reported from Acton, 1, Boston, 1, Lowell, 1, Lynn, 2, Medford, 2, Worcester, 1, total, 8.

Meningitis meningococcal was reported from Boston, 1, Middleboro, 1, Swampscott, 1, total, 3.

Meningitis Pfeiffer bacillus was reported from Boston, 1, Brockton, 1, Revere, 1, total, 3.

Meningitis pneumococcal was reported from Boston, 1, total, 1.

Meningitis other forms was reported from Mansfield, 1, total, 1.

Meningitis, undetermined, was reported from Cambridge, 3, Fall River, 1, Milton, 1, Newton, 1, Salem, 1, Wilmansett, 1, Worcester, 1, total, 9.

Poliomyelitis was reported from Chicopee, 1, Lynn, 1, total, 2.

Salmonellosis was reported from Belmont, 1, Boston, 2, Gardner, 1, Holyoke, 1, Melrose, 1, Peabody, 2, Quincy, 1, Salem, 1, Somerville, 1, Southbridge, 2, Springfield, 1, Sutton, 1, total, 15.

Septic sore throat was reported from Boston, 5, Bourne, 1, East Bridgewater, 1, Grafton, 1, Holyoke, 1, Malden, 1, Merrimack, 1, Newburyport, 1, West Newbury, 2, total, 14.

Tetanus was reported from Weymouth, 1, total, 1.

Trachoma was reported from Boston, 1, Cummingtown, 1, total, 2.

Trichinosis was reported from Boston, 5, Malden, 1, Middleboro, 1, Wenham, 2, total, 9.

Tularemia was reported from Grafton, 1, total, 1.

Typhoid fever was reported from New Bedford, 1, total, 1.

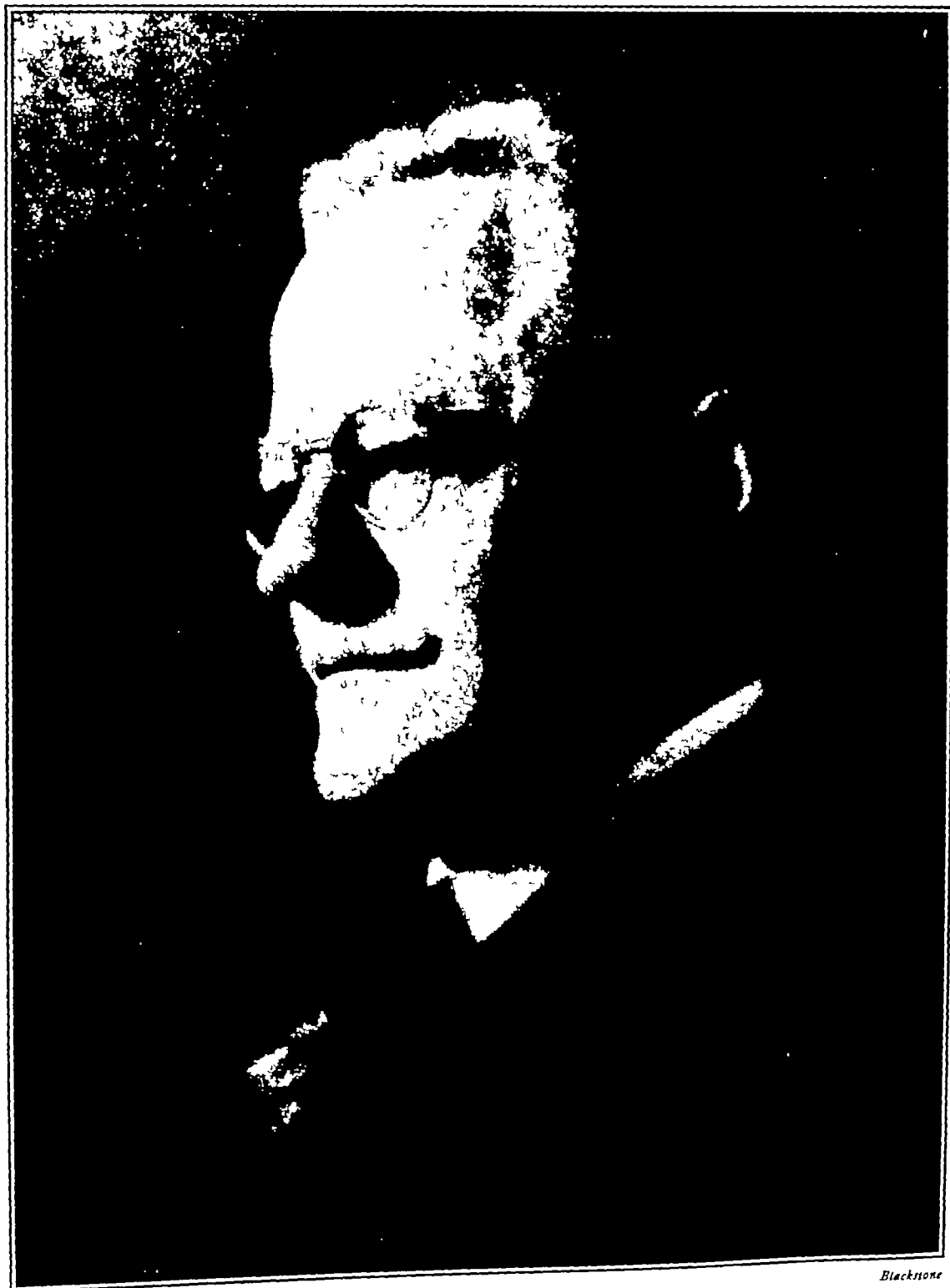
Undulant fever was reported from Adams, 1, Amesbury, 1, Auburn, 1, Dartmouth, 1, Holyoke, 1, Springfield, 1, Worcester, 1, total, 7.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

CLINIC	DATE	CLINIC CONSULTANT
Gardner (Worcester subclinic)	May 15	John W. O'Meara
Worcester	May 16	John W. O'Meara
Springfield	May 20	Garry deN. Hough Jr.
Pittsfield	May 21	Frank A. Slowick
Fall River	May 26	David S. Grice
Hyannis	May 29	Paul L. Norton

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments.

OFFICERS OF THE MASSACHUSETTS MEDICAL SOCIETY, 1946-1947

*Blackstone*DR. EDWARD P. BAGG, *President-Elect*

PROGRAM OF THE ONE HUNDRED AND SIXTY-SIXTH ANNIVERSARY OF THE MASSACHUSETTS MEDICAL SOCIETY

Monday, Tuesday, Wednesday and Thursday, May 19, 20, 21 and 22, Hotel Statler, Boston

The Registration Desk will be located on the Mezzanine Floor, and all who attend the meeting are requested to register

MONDAY AFTERNOON, MAY 19

- 4:00 Supervising Censors' Meeting (PARLOR C)
6:00 Cotting Supper for Councilors (PARLORS A AND B)

discussion by DR HARRIET L HARDY, Boston Physician, Division of Occupational Hygiene, Commonwealth of Massachusetts

- 9:30 *The Control of Respiratory Infections in Industry*
DR. GEORGE F WILKINS, Boston Assistant medical director, New England Telephone and Telegraph Company With a discussion by Dr



DR. DWIGHT O'HARA, President

Backus



DR ISAAC S F DODD, Vice-President

MONDAY EVENING, MAY 19

- 7:00 Annual Meeting of the Council (GEORGIAN ROOM)

TUESDAY MORNING, MAY 20

First General Session

GEORGIAN ROOM

- DR. DANIEL L LYNCH, *Chairman*
DR. GERALD L DOHERTY, *Co-chairman*

Symposium on Industrial Medicine

- 9:05 *Toxic Effects of Gases and Vapors* DR. MARSHALL CLYTON, Boston Associate in industrial hygiene, Harvard School of Public Health With a

ARLIE BOCK, Boston Professor of hygiene, Harvard University

- 9:55 *Rehabilitation of the Employee Injured in Industry*
DR ALEXANDER P AITKEN, Boston Medical director, Rehabilitation Center, Liberty Mutual Insurance Company, Boston With a discussion by DR AUGUSTUS THORNDIKE, JR, Boston Chief surgeon, Department of Hygiene, Harvard University

- 10:20 *Occupational Dermatoses* DR JOHN G DOWNING, Boston Professor of dermatology, Tufts College Medical School and Boston University School of Medicine

11 00 Annual Meeting of the Massachusetts Medical Society (GEORGIAN ROOM)

Annual Oration (following annual meeting) **Medical Care in Our Free Society** DR LELAND S MCKITTRICK, Boston Surgeon-in-chief, Palmer Memorial Hospital, visiting surgeon, Massachusetts General Hospital

Annual Luncheon (PARLORS A, B AND C) tickets must be procured in advance of the meeting

TUESDAY AFTERNOON, MAY 20

Second General Session

GEORGIAN ROOM

DR REGINALD FITZ, *Chairman*

DR ALBERT A HORNER, *Co-chairman*

Symposium The Distribution of Medical Care for the People of Massachusetts

2 00 *Principles of the Massachusetts Medical Society* DR ELMER S BAGNALL, Groveland Past-president, Massachusetts Medical Society

2 25 *The Contribution of the Blue Cross* MR REGINALD F CAHALANE, Boston Executive director, Massachusetts Hospital Service, Inc., and Massachusetts Medical Service, Inc., vice-chairman, Blue Cross Commission

2 50 *The Contribution of the Blue Shield* DR CHARLES G HAYDEN, Boston Medical director, Massachusetts Hospital Service, Inc., and Massachusetts Medical Service, Inc., member of the Commission, Associated Medical Care Plans

3 15 *Medical and Hospital Care of the Veterans in Massachusetts* DR WINTHROP ADAMS, Boston Branch medical director, Veterans Administration, Boston

3 40 *What Industry Thinks About the Program* MR JARVIS HUNT, North Attleboro General counsel, Associated Industries of Massachusetts, former president, Massachusetts State Senate

4 05 *Question-and-Answer Period*

TUESDAY EVENING, MAY 20

GEORGIAN ROOM

8 00 **The Shattuck Lecture** Clinical Significance of Circulatory Peculiarities of Some of the Vital Organs DR WILLIAM DOCK, Brooklyn, New York Professor of medicine Long Island College of Medicine, director of medical service, College Division, King's County Hospital

WEDNESDAY MORNING, MAY 21

Third General Session

GEORGIAN ROOM

DR ISAAC S F DODD, *Chairman*

DR ALLEN RICE, *Co-chairman*

9 00 *The Advantages of the Extraperitoneal Cesarean Section* DR ROY J HEFFERNAN, Brookline Visiting obstetrician and gynecologist, Carney Hospital,

consulting obstetrician and gynecologist, Fanner and St. Margaret's hospitals

9 25 *Diarrhea of the Newborn Its cause and prevention* DR STEWART H CLIFFORD, Boston Visiting pediatrician, Boston Lying-in Hospital, visiting physician, Infants' and Children's Hospital, instructor in pediatrics and child hygiene, Harvard Medical School

9 50 *Management of Diabetes and Its Complications* DR PRISCILLA WHITE, Boston Physician, Massachusetts Deaconess Hospital

10 15 *Cytologic Diagnosis of Carcinoma of Various Organs of the Body* DR JOE V MEIGS, Boston Chief Vincent Memorial Hospital, Massachusetts General Hospital, clinical professor of gynecology, Harvard Medical School DR MAURICE FREMONT-SMITH, Boston Associate physician, Massachusetts General Hospital, instructor in medicine, Harvard Medical School

10 40 *Ramifications of the Xanthomas* DR FRED D WELLMAN, Philadelphia Professor of research in dermatology and mycology, University of Pennsylvania School of Medicine

11 05 *A Review of Some Recently Defined Virus Diseases* DR JOHN F ENDERS, Boston Director of research, Department of Infectious Diseases, Children's Hospital, associate professor of bacteriology and immunology, Harvard Medical School

11 30 *The Uses and Abuses of Chemotherapy* DR PERRIN H LONG, Baltimore Professor of preventive medicine, Johns Hopkins University School of Medicine

WEDNESDAY NOON, MAY 21

Section Meetings and Luncheons

12 00 M — 2 00 P M

Section of Medicine

PARLOR A

DR FRANCIS C HALL, Boston, *Vice-chairman*

DR LAURENCE B ELLIS, Boston, *Secretary*

Modern Concepts of Host-Parasite Relations in Infectious Diseases DR PERRIN H LONG, Baltimore

Section of Pediatrics

PARLOR B

DR HYMAN GREEN, Boston, *Chairman*

DR GERALD N HOFFFEL, Boston, *Secretary*

Virus Diseases and the Pediatrician DR CHARLES A JANEWAY, Boston Thomas Morgan Rotch Professor of Pediatrics, Harvard Medical School, physician-in-chief, Infants' and Children's Hospital

Section of Dermatology and Syphilology

PARLOR C

DR JACOB SWARTZ, Brookline, *Chairman*

DR FRANCIS THURMON, Boston, *Secretary*

Professors in Mycological Technic DR. FREDERICK D. WEIDMAN, Philadelphia Professor in dermatologic and mycologic research, University of Pennsylvania School of Medicine

Section of Physiotherapy

HANCOCK ROOM

DR. WILLIAM D. McFEE, Haverhill, *Chairman*
DR. HENRY A. TADGELL, Belchertown, *Secretary*

Resectioning of the Arm Amputee DR. AUGUSTUS THORNDIKE, JR., Boston

A Sound Motion Picture Entitled "The Diary of a Sergeant"

WEDNESDAY AFTERNOON, MAY 21

Fourth General Session

GEORGIAN ROOM

DR. RICHARD H. SWEET, *Chairman*
DR. LOUIS H. NASON, *Co-chairman*

Symposium on Bronchiectasis

2:00 *The Pathologist Pursues the Cause* DR. TRACY B. MALLORY, Boston Director, Department of Pathology and Bacteriology, Massachusetts General Hospital

2:25 *The Roentgenologist Makes the Diagnosis* DR. HUGH F. HARE, Boston Director, Department of Radiology, Lahey Clinic

2:50 *The Physician Thinks about Treatment and Prevention on disease of the lungs, Veterans Administration, instructor in medicine, Harvard Medical School*

3:15 *The Role of Anesthesia* DR. LLOYD H. MOUSEL, Washington, D. C. Consultant to the Surgeon General, United States Army, branch section chief, Department of Anesthesiology, George Washington University School of Medicine

3:40 *The Contribution of the Thoracic Surgeon* DR. JOHN W. STRIEDER, Brookline Surgeon-in-chief for thoracic surgery, Boston City Hospital and Massachusetts Memorial Hospitals, assistant professor of thoracic surgery, Boston University School of Medicine

4:00 *Question-and-Answer Period*

WEDNESDAY EVENING, MAY 21

5:00 *Cocktail Party (SALLE MODERNE)*
Tickets must be procured in advance

7:00 *Annual Dinner of the Massachusetts Medical Society (GEORGIAN ROOM)*

Presiding

DR. DWIGHT O. HARA, president, Massachusetts Medical Society

Guest Speaker

DR. HARRISON H. SHOULDERS, president, American Medical Association The Responsibilities of the Medical Profession

Ladies may be invited to attend the dinner

Tickets for the dinner must be procured in advance of the meeting

THURSDAY MORNING, MAY 22

Fifth General Session

GEORGIAN ROOM

DR. FRANKLIN G. BALCH, JR., *Chairman*
DR. WALTER E. GARREY, *Co-chairman*

9:00 *Operating-Room Technic* DR. CARL W. WALTER, Boston Senior associate in surgery, Peter Bent Brigham Hospital, assistant professor of surgery, Harvard Medical School

9:25 *Restoration Operator for Otosclerosis* DR. PHILIP E. MELTZER, Boston Surgeon, Massachusetts Eye and Ear Infirmary, professor of otolaryngology Tufts College Medical School

9:50 *Thiouracil and Allied Drugs in Hyperthyroidism* DR. ELMER C. BARTELS, Boston Member, Department of Internal Medicine, Lahey Clinic, staff member New England Deaconess and New England Baptist hospitals

10:15 *The Disabled Veteran of World War II An analysis of 600 cases examined at Harvard University* DR. AUGUSTUS THORNDIKE, JR., Boston

10:40 *The Use of Anesthetic Drugs in Medical Practice* DR. PERRA P. VOLPITTO Augusta Georgia Professor of anesthesiology, University of Georgia School of Medicine

11:05 *Surgical Treatment of Congenital Heart Disease* DR. ROBERT E. GROSS Boston Surgeon-in-chief, Children's Hospital

11:30 *A Motion Picture Entitled "Foreign Bodies in the Heart"* With a discussion by DR. DWIGHT E. HARVEY Brookline Visiting surgeon in thoracic surgery Boston City and Cambridge hospitals, instructor in surgery, Tufts College Medical School

THURSDAY NOON, MAY 22

Section Meetings and Luncheons

12:00 M — 2:00 P M

Section of Surgery

SALLE MODERNE

DR. ALEXANDER A. J. CAMPBELL, Boston, *Chairman*
DR. GEORGE S. REYNOLDS, Pittsfield, *Secretary*

Venous Thrombosis DR. MICHAEL E. DEBAKEY, New Orleans Associate professor of surgery, Tulane University of Louisiana School of Medicine

Section of Obstetrics and Gynecology

PARLOR A

DR. WILLIAM J. McDONALD, Boston, *Chairman*
DR. ARTHUR T. HERTIG, Boston, *Vice-chairman*
DR. GEORGE VAN S. SMITH, Brookline, *Secretary*

The Treatment of Vaginal Discharge DR. CHRISTOPHER J. DUNCAN, Brookline Visiting Surgeon, Free Hospital for Women Brookline, assistant obstetrician, Massachusetts General Hospital and Boston City Hospital

Section of Radiology

TECHNICAL EXHIBITS

PARLOR C

DR EDWARD B D NEUHAUSER, Cambridge, *Chairman*
 DR HUGH F HARE, Boston, *Secretary*

The Roentgenologist and the Orthopedic Surgeon DR DAVID S GRICE, Boston Junior associate in orthopedic surgery, Children's Hospital and Peter Bent Brigham Hospital, assistant in orthopedics, Harvard Medical School

Section of Anesthesiology

PARLOR B

DR SIDNEY C WIGGIN, Waban, *Chairman*
 DR MORRIS J NICHOLSON, Boston, *Secretary*

Standardization of the Economics of Anesthesia DR PERRY P VOLPITTO, Augusta, Georgia

THURSDAY AFTERNOON, MAY 22

Sixth General Session

GEORGIAN ROOM

DR HOWARD F ROOT, *Chairman*
 DR GORDON M MORRISON, *Co-chairman*

2 00 *Anticoagulation Treatment of Postoperative Venous Thrombosis and Pulmonary Embolism* DR JAMES A EVANS, Boston Physician, Lahey Clinic, physician, New England Baptist and New England Deaconess hospitals

2 25 *Thrombophlebitis and Phlebothrombosis* DR MICHAEL E DEBAKEY, New Orleans

2 50 *The Practical Importance of Modern Concepts of Psychosomatic Relations* DR ALFRED O LUDWIG, Boston Assistant psychiatrist, Massachusetts General Hospital, staff psychiatrist, Robert Breck Brigham Hospital, consultant, Office of the Surgeon-General Veterans Administration

3 15 *The Clinical Effectiveness of Transthoracic Vagus Resection in the Treatment of Peptic Ulcer* DR FRANCIS D MOORE, Boston Assistant in surgery, Massachusetts General Hospital, associate in surgery, Harvard Medical School

3 40 *The Services Offered to the Physician by the Massachusetts Department of Public Health* DR VLADO A GETTING, Boston Commissioner, Department of Public Health, Commonwealth of Massachusetts

4 05 *The Present-Day Status of Poliomylitis* DR WILLIAM T GREEN, Boston Chief, Orthopedic Service, Children's Hospital, clinical professor of orthopedic surgery, Harvard Medical School

4 30 *Recent Trends and Treatment in Allergy* DR WALTER S BURRAGE, Boston Assistant physician, Massachusetts General Hospital, allergist, Newton-Wellesley Hospital, chief of allergy, Branch No 1, Veterans Administration

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 Alkalol Company
 Ames Company, Inc
 Ayerst, McKenna & Harrison, Ltd
 Ba-Bee Dietary Service, Inc
 Chester Baker, Inc
 Baker Laboratories
 Bard-Parker Company, Inc
 Best Foods, Inc
 Bilhuber-Knoll Corp
 The Borden Company
 Boston Medical Supply Company
 Brewer & Company, Inc
 Bristol Laboratories, Inc
 Buffington's, Inc
 Burroughs Wellcome & Company
 Cambridge Instrument Company, Inc
 Camel Cigarettes
 Certified Milk Producers Association
 Ciba Pharmaceutical Products, Inc
 Coca-Cola Bottling Company
 Crosbie-Macdonald Company
 Davies, Rose & Company, Ltd
 Denver Chemical Company
 Doho Chemical Corp
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 C B Fleet & Company
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 Gerber Products Company
 J E Hanger, Inc
 Hanovia Chemical & Mfg Company
 Harper-Wallins Corporation
 Harper X-Ray Corporation
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 National Dairy Products Company
 The National Drug Company
 Nestle's Milk Products, Inc
 T J Noonan Company
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 E L Patch Company

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Pitman-Moore Company	84
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Pure Chemicals, Incorporated	81
L. & B. Reiner	33
Saborn Company	71
Sandoz Chemical Works, Inc.	42
Science Corporation	41
G. D. Searle & Company	24
Sharp & Dohme, Inc	30
Smith, Kline & French Laboratories	8
Spencer, Inc.	17
E. R. Squibb & Sons	73
Friedrich Stearns & Company	47 & 48
Sutro's & Physicians Supply Company	30
Swift & Company	91
Talby-Nason Company	17
U. S. Vitamin Corporation	93
Vapocelina Company	6
Walker Vitamin Products, Inc	90
Westinghouse Electric Corporation	1 & 2
White Laboratories, Inc	36 & 37
Widrop Chemical Co., Inc	55
Wyeth, Incorporated	88
F. E. Young & Company	26

CORRESPONDENCE

DIGITALIS

To the Editor Another excellent article on medical progress, namely "Digitalis," by Drs. Freedberg and Zoll, appeared in the December 6, 1946, issue of the *Journal*. A paragraph gives emphasis as an example of the unsatisfactory state of our knowledge concerning one of our most extensively studied and generally used drugs. It states:

One cat unit is defined as the amount of digitalis per kilogram of cat weight that produces a lethal effect under certain defined conditions. One *USP XII* unit of digitalis represents the same potency as 0.1 gm. of the *USP* digitalis reference standard powder, when assayed as directed. The digitalis leaves from which the reference powder was made, however, were of high potency, so that 1 *USP XII* unit is equivalent to 20 per cent more than 1 cat unit. It is particularly important for the physician to know the digitalis preparation he is using since the clinical effect of digitalis, standardized according to *USP XII*, is approximately 25 per cent weaker than *USP XI*, which in turn is approximately 50 per cent stronger than *USP A*.

In reading the article one also learns that the cat method of assay measures the lethal potency of digitalis and not specific therapeutic action, also that by comparative assays in cats and human beings, a group of digitalis preparations with the same strength in cat units showed a tenfold range in potency in human subjects.

This, obviously, is hardly a satisfactory standardization of a therapeutic agent. Perhaps it is somewhat natural, therefore, for those of us who are not cardiologists to ask why we continue to perplex physicians with cat units and complicated discussions of digitalis therapy when a crystallized digitaline has been available since 1866 that is a thousand times as therapeutically effective as digitalis leaf and has certain other advantages. Quoting again from the same progress article:

In summary, the advantages of digitoxin are that it is a pure chemical that is stable and does not require bioassay and that it is completely absorbed from the gastrointestinal tract, so that oral and intravenous doses are the same and interchangeable. Furthermore the small amount of digitoxin necessary for digitalization permits administration of a large fraction in a single dose, with only a small incidence of local gastrointestinal irritation. The rapid onset of action makes for quick digitalization by the oral route

so that intravenous administration is rarely necessary. The prolonged duration of action, like that of whole-leaf digitalis, makes for easy maintenance. It is thus the drug of choice when a purified preparation is desired.

Is it naïveté or common sense that also leads the non-cardiologist to ask when a purified preparation is not desirable?

If the answer is one of expense this could be overcome by an increased demand by physicians for the pure product. If it is because of conservative reverence for a time-tested therapeutic agent the seventy years of digitoxin would appear to remove that product from the classification of *rosaliaux*.

ALLAN M. BUTLER, M.D.
Massachusetts General Hospital
Boston

UNLAWFUL IMPORTATION OF NARCOTIC DRUGS

To the Editor From time to time the Bureau of Narcotics and the Bureau of Customs have received complaints from physicians when narcotic drugs have been seized from their medical bags at the time of re-entering the United States from a visit to Mexico or Canada.

In view of the above fact the Commissioner of Narcotics has requested the following notice be printed in medical journals of states close to either Canada or Mexico:

Under the provisions of the Narcotic Drugs Import and Export Act it is unlawful for a physician to carry narcotic drugs in his medical bag back and forth between the United States and Mexico and between the United States and Canada. Narcotic drugs found in the possession of a physician on returning to the United States are seized and forfeited. Because of lack of knowledge of the law many physicians are caused embarrassment and inconvenience when traveling between this country and Mexico or Canada. This information is published in order that physicians may be correctly informed with reference to this provision of the federal law.

P. A. WILLIAMS
District Supervisor

District Office
Bureau of Narcotics
P. O. Box 2138
Boston 6

BOOK REVIEWS

Public Health and Welfare Reorganization: The postwar problem in the Canadian provinces. By Harry M. Cassidy, Ph.D. 8°, cloth, 464 pp. Toronto: Ryerson Press, 1945. Cloth \$4.50, paper \$3.50.

This work is a sequel to the author's *Social Security and Reconstruction in Canada*, published in 1943. The text is divided into four parts. The first discusses premises for provincial planning, with an analysis of the present system and suggested adjustments in the provincial systems. The second and third are devoted to British Columbia, the Prairie provinces, Ontario, Quebec and the Maritime provinces. The history of public health in these localities, the present status and suggested programs for the future are considered in detail. The fourth part is a summary pointing out the flaws in the present system and outlining the principles of reorganization. The importance of local units and national leadership is stressed.

On the basis of his practical experience and study the author is convinced that there are serious weaknesses in the Canadian provincial and local social services, including the health services. He believes that drastic changes in organization and administration are required before these services can reach high standards.

This document should be in all public-health collections.

Clinical Roentgenology of the Heart. By John B. Schwedel, M.D. *Annals of Roentgenology*, Volume XVIII. 4°, cloth, 380 pp., with 749 illustrations. New York: Paul B. Hoeber, Incorporated, 1946. \$12.00.

This volume presents a brief summary of the present status of the roentgenologic study of the heart and great vessels.

There are many illustrations, including not only roentgenograms but also diagrams and photographs of pathological specimens. The text is clear, the pictures are well selected, and the volume is well printed and bound. Of particular interest is the emphasis on normal variations in Chapter 4.

As in any brief work of the sort, some things are too much abbreviated. It would be of value to add illustrations of a dissecting aneurysm of the aorta, both before and after its development. A more typical illustration of constrictive pericarditis is also desirable and, similarly, a roentgenogram of the heart showing auricular septal defect without mitral stenosis. Tricuspid atresia might well have been added as one of the more newly recognizable congenital defects. It should be noted that, on occasion, funnel chest may compress as well as displace the heart and thus embarrass the circulation.

The electrocardiogram reproduced in Figure 53J on page 90 is upside down, as is that in Figure 72C on page 128. In the last sentence of page 319 "left" should read "right."

This book can be recommended as an up-to-date exposition of roentgenology of the heart and great vessels.

It's How You Take It By G. Colket Caner, M.D. 12°, cloth, 152 pp. New York: Coward-McCann, Incorporated, 1946. \$2.00.

Physicians will find this book a practical volume to recommend to patients as an adjunct to psychotherapy. A troubled person can read it without risk and can find in it pertinent discussion of problems closely related to his own, and a healthy person can gain through it understanding that will enable him to function at a higher level of effectiveness and contentment. The book is concise, simple and free from technical language.

The literary device of posing questions, used in the book, stimulates interest and attention. Dr. Caner's answers, which are constructive and replete with wholesome ideas, make clear what a person can do toward helping himself. They give an understanding of psychosomatic reactions and of the effect of various attitudes on relations with others and on emotional stability. The common sense and idealism of the book make it particularly suited to young persons but it will also appeal to adults particularly to parents and teachers. The volume could be profitably used in high schools as a basis for the teaching of mental hygiene, whose preventive aspects it covers thoroughly and soundly. It is a book to be studied and to be read thoughtfully over and over again. Used in this way, it will be extremely helpful.

Diseases of the Adrenals By Louis J. Soffer, M.D. 8°, cloth, 304 pp., with 42 illustrations and 2 colored plates. Philadelphia: Lea and Febiger, 1946. \$5.50.

This book is constructed along orthodox lines and covers the adrenal gland from medulla to cortex. One of its most valuable features is an account of methods now in use for determining the concentrations of sodium or potassium in serum and urine and for assaying the excretion of androgens, estrogens and 17-ketosteroids. The part of the monograph that describes Addison's disease and the clinical manifestations of the different tumors that may involve the adrenal glands is well written. The color plates are excellent. On the whole, the volume represents much industry and can be recommended as a useful work of reference.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Mongolism and Cretinism. A study of the clinical manifestations and the general pathology of pituitary and thyroid deficiency. By Clemens E. Benda, M.D., director, Wallace Research Laboratory for the Study of Mental Deficiency, Wrentham, Massachusetts, instructor in neuropathology, Harvard Medical School, and assistant in psychiatry, Mas-

sachusetts General Hospital. 8°, cloth, 310 pp., with 10 illustrations and 48 tables. New York: Grune and Stratton, 1946. \$6.50.

Dentistry. An agency of health service. By Malcolm W. Carr, D.D.S., director of oral surgery and visiting oral surgeon, Metropolitan Hospital, attending oral surgeon, St. Luke's Hospital, Knickerbocker Hospital, Polyclinic Hospital and Flower and Fifth Avenue Hospitals, consultant oral surgeon, Roosevelt Hospital, and lecturer in oral surgery, Graduate School of Medicine, University of Pennsylvania. Studies of the New York Academy of Medicine, Committee on Medicine and the Changing Order. 8°, cloth, 216 pp. New York: The Commonwealth Fund, 1946. \$1.50.

Jerome Carden By James Eckman. 4°, paper, 120 pp. Baltimore: Johns Hopkins Press, 1946. \$2.00.

Eight Years of Public Health Work. Jones County, Mississippi 1937-1944. By Harry E. Handley, M.D., assistant director, Division of Public Health, The Commonwealth Fund, and Carolina R. Randolph, director of studies, Division of Public Health, The Commonwealth Fund. 12°, paper, 80 pp., with 47 tables. New York: The Commonwealth Fund, 1946. 50 cents.

Modern Development of Chemotherapy. By E. Havinga, H. W. Julius, H. Veldstra, and K. C. Winkler. 8°, paper, 175 pp., with 31 illustrations and 8 tables. New York: Elsevier Publishing Company, Incorporated, 1946. \$3.50.

Autopsy, Diagnosis and Technique. By Otto Saphir, M.D., pathologist, Michael Reese Hospital, and professor of pathology, University of Illinois Medical School, Chicago. With a foreword by Ludwig Hektoen, M.D. Second edition, revised and enlarged. 12°, cloth, 405 pp., with 69 illustrations. New York: Paul B. Hoeber, Incorporated, 1946. \$5.00.

Medicine in Industry. By Bernhard J. Stern, Ph.D., lecturer in sociology, Columbia University, and visiting professor of sociology, Yale University. Studies of the New York Academy of Medicine. Committee on Medicine and the Changing Order. 8°, cloth, 209 pp. New York: The Commonwealth Fund, 1946. \$1.50.

The Diagnosis and Treatment of Pulmonary Tuberculosis. By Moses J. Stone, M.D., assistant professor in medicine, Boston University School of Medicine, instructor in medicine, Tufts College Medical School, and physician-in-chief, Chest Clinics, Beth Israel and Massachusetts Memorial Hospitals, and Paul Dufault, M.D., superintendent, Rutland State Sanatorium, Rutland, Massachusetts. With a foreword by Henry D. Chadwick, M.D. 12°, cloth, 325 pp., with 93 illustrations. Philadelphia: Lea and Febiger, 1946. \$3.50.

Mother and Baby Care in Pictures. By Louise Zabriskie, R.N., director, Maternity Consultation Service, New York City, lecturer, New York University, and field director, Maternity Center Association, New York City. Third edition, modernized. 8°, cloth, 203 pp., with 229 illustrations and 7 tables. Philadelphia: J. B. Lippincott Company. \$2.00.

Complete Handbook on State Medicine. By J. Weston Walch. 4°, paper, 170 pp. Portland, Maine: J. Weston Walch, 1946. \$2.50.

NOTICES

ANNOUNCEMENTS

Dr. Harrison E. Kennard announces the reopening of his office at 374 Marlborough Street, Boston, for the practice of general surgery.

Dr. Robert C. Thompson announces the opening of his office at 293 Humphrey Street, Swampscott, for the practice of general medicine and surgery.

(Notices continued on page xviii)

The New England Journal of Medicine

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Volume 236

MAY 15, 1947

Number 20

BACTERIAL ENDOCARDITIS TREATED WITH PENICILLIN*

Observations in Nine Cases

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BOSTON

THE unprecedented cures of subacute bacterial endocarditis with penicillin have stimulated fresh interest in this heretofore fatal disease. During the last two years 9 patients have been treated and followed at the Lahey Clinic. The abstracts of these cases are presented for several reasons: unusual organisms were encountered in 2, surgery was instrumental in curing 1, and 1 represented the bacteria-free stage of bacterial endocarditis. The need for individualization of treatment is demonstrated, and several suggestions are made for improving present-day results.

CASE 1 A 59-year-old clerk was admitted to the hospital on January 1, 1946. He complained of weakness and subternal discomfort of 2 years' duration and a loss of 16 pounds in weight during the previous 2 months. For 6 months occasional temperature elevations had occurred. There was no history of rheumatic fever or syphilis.

Physical examination showed a pale and sickly patient with moderate pitting edema of the ankles. Slight exertion caused dyspnea. A to-and-fro murmur, loudest at the aortic area, and accentuation of the pulmonic second sound were detected. The cardiac apex was in the anterior axillary line in the sixth intercostal space. The blood pressure was 170/40 to 0, and the pulse was of water-hammer type. Other findings were basal pulmonary rales, petechiae, clubbing of the fingers, splenomegaly and tremor of the head and hands. The patient was given digitalis and a salt-free diet and kept in bed. There was no fever until the 8th day, when the temperature rose to 101°F.

Streptococcus mutraceus was isolated from the blood. There was a mild hypochromic anemia with a normal number of leukocytes, 47 per cent of which were young forms. Blood Hinton, Kahn and Wassermann tests were negative. Urinalyses showed no abnormal findings. The blood non-protein nitrogen was 35.8 mg. per 100 cc. Roentgenograms showed enlargement of the heart in all dimensions, congestion of the lungs and no dental infection. Electrocardiograms revealed a sinus rhythm, left-axis deviation, and occasional extrasystoles.

Figure 1 illustrates the penicillin and sulfadiazine blood levels and the results of blood cultures and penicillin sensitivity tests correlated with the temperature chart. The response to penicillin was dramatic. The temperature rapidly returned to normal, and the blood cultures became sterile. Concurrent heart failure progressed, however, in spite of digitalization, avoidance of sodium, an acid-ash diet and

mercurial diuretics. The patient left the hospital on the 40th day to convalesce nearer home, and 10 days later died from heart failure. Autopsy was not performed.

The value of determining both the penicillin sensitivity of the organism and the penicillin blood levels was confirmed in this case. Had the usual arbitrary doses been used without knowledge of these two determinations, insufficient penicillin would have been administered. Intramuscular administration resulted in a rapid decrease of penicillin in the blood—from 5 units per cubic centimeter an hour after injection to 0.65 units three hours later. Constant intravenous administration gives constant blood levels¹ and appears to be more efficient.

Streptococcus mutraceus, a variety of *Str. bovis*, is rarely reported in subacute bacterial endocarditis. Its true incidence in this disease cannot be determined, since bacteriologic studies are not usually made to identify individual members of the *Str. viridans* group. The strain isolated from this case proved to have a moderately high penicillin resistance.

With three negative blood cultures before discharge, presumably the infection was eradicated, but final conclusions regarding cure are not justified, since death from heart failure prevented a satisfactory period of observation. The rapid progression of heart failure after the institution of penicillin therapy in a patient digitalized and resting in bed, when previously he had not been receiving digitalis and had been moderately active, raises the question of the possible toxicity of penicillin for the myocardium. Electrocardiograms, however, failed to show any significant changes during treatment. Another possibility is that valvular changes from healing processes increased myocardial strain.

CASE 2 A 34-year-old housewife and secretary entered the hospital on September 1, 1944, with fever and malaise. There was no history of rheumatic fever. The illness had begun 16 months previously with a temperature of 104°F and generalized aching. Petechiae and a loud apical systolic murmur were found but repeated blood cultures were sterile. An

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intradermal test for undulant fever showed whealing, whereas agglutination tests for brucellosis were negative. There was no history of drinking of raw milk in recent years, and neighborhood herds of cows tested by the Vermont State Health Department were found free of Bang's disease. The blood sedimentation rate was 93 mm in 1 hour. A roentgenogram showed slight cardiac enlargement. A diagnosis of subacute bacterial endocarditis due to *Brucella abortus* was made, and the patient was given blood transfusions and injections of brucellergin. Only temporary improvement occurred, and sulfadiazine and arsenicals were unsuccessfully used. Intravenous injections of typhoid vaccine failed to cause a rise in temperature. Repeated blood cultures were sterile, and the sedimentation rate varied between 40 and 100 mm in 1 hour. Just before admission the patient had been

Few cases of bacterial endocarditis due to *Br. abortus* have been reported, and no satisfactory treatment has evolved. Trial with modern anti-bacterial substances failed in this case. Streptomycin appears to be of value in some cases of brucellosis,² but its final evaluation in this infection awaits future study, the drug was not available for use in this case.

No explanation is apparent for the isolation of five different bacterial species from the patient's blood. Mixed infection is not usually encoun-

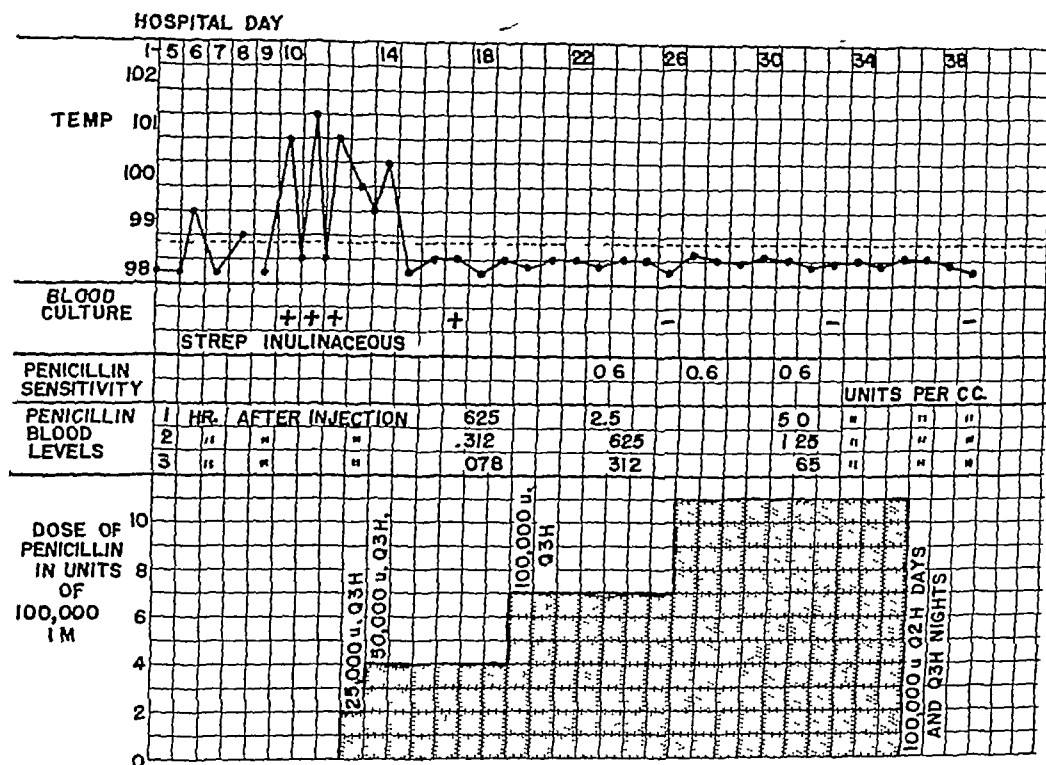


FIGURE 1 Summary of Data in Case 1

given a total of 2,000,000 units of penicillin intramuscularly at intervals of 3 hours for 7 days.

On admission the patient did not appear ill, but she had lost 19 pounds. A loud apical systolic murmur was noted. There was no enlargement of the spleen or clubbing of the fingers. A gram-negative bacillus identified as *Br. abortus* was grown in four cultures, hemolytic *Staphylococcus aureus* on four, a diphtheroid on one and hemolytic and nonhemolytic staphylococci and gram positive bacilli on one, six cultures were sterile. The staphylococci were all coagulase negative and may therefore have been contaminants. Agglutination tests with the patient's serum and stock vaccines of *Brucella* organisms failed to show agglutination. The patient's serum agglutinated the isolated gram-negative bacilli in a titer of 1:5120. Urinalyses showed pyuria, and hemograms, a mild hypochromic anemia. A blood Hinton test was negative.

The following treatment failed to sterilize the blood stream: 400,000 units of penicillin intravenously daily for 19 days, sulfadiazine, which effected a blood level of 6 to 17.5 mg. per 100 cc. for 10 days, and sulfamerazine with a blood level of 11.2 to 15.8 mg. per 100 cc. for 12 days. The patient was discharged unimproved.

tered in bacterial endocarditis, and the question arises whether brucellosis predisposes to such a condition.

CASE 3 A 21-year-old housewife was first seen on July 25, 1944, because of dysuria and urinary frequency of 3 days' duration. A similar episode had occurred several months previously, and had responded to sulfonamide therapy. A cardiac murmur had been known to have been present since early childhood.

Physical examination disclosed a machine-like murmur and thrill over the pulmonic-valve area and cardiac enlargement to the left. The blood pressure was 120/40. Roentgenologic study revealed fullness of the left border of the heart in the region of the pulmonary conus. The transcardiac diameter was 13 cm., and the transthoracic 24.4 cm. The urine contained numerous pus cells, and a urogram showed a double ureter on the right. The urinary infection responded to sulfathiazole and subsided uneventfully. The patient was advised to have a right ureterectomy and ligation of the ductus arteriosus, but refused operation.

She remained well until 10 months later, when there developed fever, headache, arthralgia and myalgia, which did not respond satisfactorily to sulfadiazine administration at home, and on May 28, 1945, she was admitted to the hospital. In addition to the previous findings, she had a temperature of 100°F, herpes labialis and marked pallor. The blood pressure was 150/20. The blood sedimentation rate, previously normal, was 45 mm in 1 hour. Three blood cultures grew *Str. viridans*; one showed 28 colonies per cubic centimeter of blood. The circulation time was 25 seconds with Decholin and 8 seconds with ether. The venous pressure was equivalent to 80 mm of water. An electrocardiogram showed a diphasic T wave in Lead I and a prominent Q wave in Lead 3.

The patient was given 200,000 units of penicillin intramuscularly daily for 7 days, and the blood stream became sterile. Dr. Ralph Adams then ligated and resected the patent ductus arteriosus. Following operation, 40,000 units of penicillin was given intramuscularly every 3 hours for 3 weeks, and blood cultures remained sterile.

Shortly before discharge, roentgenographic studies showed the pulmonary conus to be less prominent, and the aortic arch to be slightly wider. An electrocardiogram revealed prominent Q waves in Leads 2 and 3 and increased voltage of the T waves in all leads. A faint systolic murmur persisted at the pulmonic area. The patient left the hospital on June 30.

A month later she was admitted to an out-of-town hospital because a blood culture had been found to contain a few colonies of *Str. viridans*, and although subsequent cultures were negative, a total of 4,000,000 units of penicillin was given. A letter from her physician reported her to be well and free of any signs of infection 22 months later.

It is not unusual for patients with a patent ductus arteriosus to develop blood-stream infection. Abbott³ found such a complication in 21 of 92 patients with this congenital heart lesion. Only recently has the combined use of surgical ligation and penicillin changed the fatal outcome. In suitable patients the best time to carry out operation is before infection has occurred, both to prevent subsequent endarteritis or endocarditis and to protect the heart from further strain. The largest series of cases is that of Gross,⁴ who reported successful division of the ductus arteriosus in 14 patients, 2 of whom had a superimposed *Str. viridans* endocarditis.

CASE 4. A 45-year-old silver-press foreman was admitted to the hospital on December 12, 1944. There was no history of rheumatic fever. Five months previously anorexia, weight loss, fever, chills and soreness of the fingertips had developed. Pneumonia was suspected, and treatment with sulfathiazole earned out. The patient improved, but the temperature continued to be elevated, spiking to 106°F. Numerous blood cultures and one bone-marrow culture were sterile. He was given penicillin in doses unknown to us for 18 days and is said to have shown improvement. No further therapy was used for the next 3 months.

On admission the patient appeared to be extremely ill. He had lost 20 pounds in weight. A café au lait color was noted. There was marked dental sepsis. A Grade III diastolic murmur heard in the left parasternal line was loudest in the 3rd costal interspace. Rales were detected in the lung bases. The fingers were clubbed, and the edge of the spleen extended 5 cm below the costal margin, but there were no petechiae.

Twelve blood cultures were sterile. A bone-marrow biopsy grew a nonhemolytic pleomorphic anaerobic streptococcus. Agglutination tests for undulant and typhoid fever gave negative results. Examination of the blood showed a mild hypochromic anemia, a normal number of leukocytes and a slight increase in the percentage of young cells. Urinalysis and a blood Hinton test were negative. X-ray examination disclosed that the heart was enlarged in all diameters, and the lungs were clear.

For 6 days the patient was given sulfadiazine to maintain a blood level of 12.8 to 14.8 mg per 100 cc., with dicumarol to reduce the prothrombin time of the blood to 48 to 77 per cent of normal. Three transfusions were given, and for the last 6 days of his life he received 400,000 units of penicillin daily by constant intravenous drip.

The fever remained intermittent, with peaks to 101°F. The murmur did not change until the day before death, when it was notably louder. The patient's condition continued to deteriorate uninfluenced by therapy, and he died 37 days after admission.

Autopsy. Post-mortem examination showed moderately sclerotic aortic cusps. The posterior cusp was torn at its left attachment to the aorta. Microscopically, there was fibrin at the tip of one of these cusps, and between the meshes of fibrin were leukocytes and a homogenous red substance. A Gram-Weigert stain was made, but no bacteria were identified. Near the base of one cusp there was an area about half the size of a low-power field filled with congested blood vessels and rather heavily infiltrated by polymorphonuclear leukocytes and lymphocytes. In the neighboring endocardium and sub-endocardium of the heart wall there was diffuse infiltration with polymorphonuclear leukocytes—in some places to the extent of forming small true abscesses. Other significant autopsy findings were congestive heart failure, extramedullary hematopoiesis and focal embolic glomerulonephritis.

This case represents the bacteria-free stage of bacterial endocarditis. Numerous blood cultures on special mediums failed to grow organisms, and special studies at autopsy failed to demonstrate bacteria. The significance of organisms isolated from the bone marrow is doubtful, for bacteria may lie dormant in the marrow for long periods with no relation to blood-stream infection.⁵ The fever in bacteria-free cases may be due to multiple small emboli similar to those found at autopsy in the kidney. Such a case is predestined to therapeutic failure with antibacterial substances, since bacteria are no longer responsible for the illness. It is possible that a prolonged period of anticoagulant therapy in these cases would prevent thrombi from forming on the heart valves and further embolization until healing had occurred.

CASE 5. A 42-year-old teacher entered the hospital on June 16, 1944, for decision regarding the need of further therapy. Two months before admission he had begun having gripe-like symptoms, elevations of temperature, occipital pains, paresthesias of the right arm and face and vomiting. He was hospitalized elsewhere, and blood cultures were taken. The thirteenth grew *Str. viridans*. One million one hundred thousand units of penicillin was given by constant intravenous drip from May 27 to June 4. Two days later the fever recurred, and urticaria appeared. Penicillin was again started, and from June 7 to June 16, a total of 28,000 units was given intramuscularly every 3 hours. Both the fever and the urticaria disappeared shortly after this second course had been instituted.

On admission the patient was asymptomatic. Early clubbing of the fingers was noted. The blood pressure was 120/70. A presystolic murmur and a snapping first sound were heard at the apex of the heart. There was no splenic enlargement, petechiae, dental sepsis or joint pains. The temperature and pulse remained normal.

Six blood cultures showed no growth. Urinalysis and a blood Hinton test were negative, and a hemogram, electrocardiogram and roentgenogram of the chest were normal. The blood sedimentation rate was 54 mm in 1 hour. No further treatment was deemed necessary.

In a follow-up letter 25 months after discharge a physician stated that the patient had remained perfectly well. There had been no sign of recurrence, but as an added precaution he had been hospitalized on three occasions at intervals of 6 months for a course of 1,000,000 units of penicillin.

It is noteworthy that the diagnosis was made early in this case. Although only moderate doses of penicillin over a relatively short time were used, the patient remained cured twenty-three months later. It is doubtful that the subsequent courses of penicillin were needed, since at no time was there any sign of recurrence. An interesting observation is the occurrence of urticaria shortly after the first course of penicillin, and its disappearance soon after institution of the second course. That the sedimentation rate of the blood does not determine cure is shown by its elevation even after cure had been established. Goerner, Geiger and Blake⁶ have reported its persistent elevation in some cases for more than six weeks.

CASE 6. A 57-year-old woman entered the hospital on May 10, 1944. In childhood she had had rheumatic fever. Six months before admission there had been fleeting joint pains and a low-grade fever that did not respond to salicylate therapy. Two blood cultures grew *Str. viridans*. In spite of satisfactory concentrations of sulfadiazine in the blood, cultures remained positive, temperature elevations continued and occasional petechiae were found.

Physical examination disclosed a *cafe au lait* color, a rim of fine new pink skin at the nail bases, indicative of early clubbing, a systolic murmur at the apex heard only in the left lateral position, an accentuated apical first sound, carious teeth, a tender, red swelling of the left instep and tenderness of the right elbow. The patient had lost several pounds in weight but did not appear acutely ill. There was no splenic enlargement, and the lungs were clear. Roentgenograms of the chest showed no cardiac enlargement. The blood sedimentation rate was 79 mm in 1 hour. Blood cultures grew *Str. viridans*. Urinalyses were negative, and hemograms normal.

One million units of penicillin was given by constant intravenous drip during the next 10 days, followed by 12,500 units intramuscularly every 3 hours for another 10 days. There was clinical improvement, with remission of the fever and disappearance of the joint pains. The heart murmur increased in intensity. The sedimentation rate dropped to 48 mm in 1 hour, and the patient was discharged.

Shortly after her return home she suffered a relapse that was treated with 2,000,000 units of penicillin. A report, 24 months later, stated that she was perfectly well.

This patient was the first to be treated with penicillin at the clinic, and supplies were scarce. The successful outcome, like that in Case 5, proves that an occasional patient with bacterial endocarditis responds satisfactorily to small doses of penicillin given over a relatively short time. Nevertheless, now that penicillin is plentiful, large doses over a long period should be used to allow a good margin of safety. If relapse occurs, further treatment may be successful, as in this patient. The change in the intensity of the heart murmur under treatment suggests structural change in the valve as a result of healing of the infected cusps.

CASE 7. A 32-year-old machinist was admitted to the hospital on December 29, 1944, because of polydipsia, polyuria, fever, chills, diarrhea and malaise of 7 days' duration. In 1934 he was said to have had hematuria and similar symptoms. Blood cultures taken elsewhere were reported to have grown gram-positive staphylococci and streptococci. A total of 470,000 units of penicillin had been given intramuscularly by a physician.

Physical examination revealed no signs of bacterial endocarditis other than petechiae. A chest roentgenogram was normal. The urine contained a trace of albumin, and the sediment showed occasional red and white cells. Examination

of the blood was negative, except for a white-cell count of 12,500. The blood sedimentation rate was 100 mm in 1 hour. A blood culture taken soon after admission showed a coagulase-positive *Staph. aureus*.

The patient was given 20,000 to 30,000 units of penicillin intramuscularly every 2 hours, and 2,420,000 units was administered during the next 32 days. The temperature varied from 99 to 103.6°F, and the urine continued to show blood cells and casts. The white-cell count remained between 10,000 and 20,000. The heart sounds remained normal until January 6, when a systolic murmur and thrill were found in the aortic area, and a diastolic murmur over the entire precordium. Three days later the patient developed acute pulmonary edema, which responded to atropine. On January 20 a pericardial friction rub was heard, 2 days later he developed pulmonary edema and died.

Autopsy. The significant findings included subacute bacterial endocarditis of the aortic valve, cardiac hypertrophy and dilatation, serofibrinous pericarditis, a recent splenic infarction, acute glomerular nephritis and congestive heart failure. Microscopical examination of firm, white nodules from the aortic valve showed fibrosis, hyalinization and infiltration by leukocytes, with a predominance of polymorphonuclear cells.

The custom of calling bacterial endocarditis acute if it has been present for less than six weeks and subacute after it has persisted six weeks or longer has less significance than heretofore. In cases that would formerly have been called subacute, penicillin often arrests the illness before it has lasted six weeks, and may prolong the course of the acute type beyond this period. A better way of classifying bacterial endocarditis is by indication of the causative organism, as in pneumonia. This case exemplifies the difficulty of distinguishing acute from subacute disease, since the clinicians considered it acute whereas the pathologists thought it subacute. We have preferred to classify it as bacterial endocarditis due to *Staph. aureus*.

CASE 8. A 28-year-old housewife entered the hospital on October 10, 1945. She had had rheumatic fever in childhood and again at the age of 22. Seventeen months before admission, she had had a sore throat and cystitis, both of which had responded rapidly to sulfonamide therapy, but malaise and a low-grade fever had continued. In August there were migratory joint pains and petechiae. Repeated blood cultures were positive for *Str. viridans*. Penicillin, heparin and sulfadiazine were administered unsuccessfully, and for 11 months the patient gave herself 15,000 units of penicillin intramuscularly every 3 hours day and night. In March a sharp pain in the left lumbar region was diagnosed as renal infarction, and in May a chest pain was called pulmonary embolism. Blood cultures remained positive, but the fever well and for 2 months before admission remained afebrile. On the day before entry she experienced a severe bilateral headache with nausea and vomiting. Cerebral embolism was suspected.

Physical examination disclosed a well nourished woman whose weight had been increasing slightly and who did not appear acutely ill. Significant findings were a temperature of 101°F, cardiac enlargement, an apical systolic murmur widely transmitted, a diastolic murmur over the left 3rd and 4th costochondral junctions and *Str. viridans* on blood culture. There were no petechiae, finger clubbing or splenic enlargement. A spinal puncture demonstrated normal dynamics of the fluid, with 297 polymorphonuclear leukocytes per cubic millimeter, a culture of the fluid was sterile. The headache disappeared after this examination, and late specimens of spinal fluid showed no leukocytosis.

Urinalyses showed a trace of albumin, and hemograms, mild hypochromic anemia, a blood Hinton test was negative. The blood sugar and nonprotein nitrogen determinations were normal.

Three hundred thousand units of penicillin was given by constant intravenous drip daily for 6 days, 200,000 units for 3 days, and 320,000 units for 2 days. A sulfadiazine blood level of 9.1 mg per 100 cc. was maintained for 12 days. On discharge the patient was instructed to take 15,000 units of penicillin intramuscularly every 3 hours.

One week later two or three colonies of *Str. viridans* per cubic centimeter of blood were found, and an additional 3,000 units of oral penicillin every 3 hours was prescribed. A few days later the temperature rose to 100.8°F and there were fresh petechiae so that 1 gm of sulfadiazine every 4 hours was added.

The patient re-entered the hospital on November 21, and was given 500,000 units of penicillin daily by constant intravenous drip for the next 5 weeks. Three blood cultures were negative before discharge on December 28. She continued to give herself 25,000 units of penicillin intramuscularly every 3 hours. Blood cultures remained sterile, but the blood sedimentation rate continued to be elevated and a low-grade fever persisted. On July 10, 1946, when last examined, she had gained 15 pounds in weight and felt well. The blood sedimentation rate was 66 mm in 1 hour. Approximately 100,000,000 units of penicillin had been given during the previous 19 months.

Therapy with relatively large doses of penicillin for five weeks and with moderate doses for seventeen months failed to bring about a cure, although such treatment suppressed the infection and prevented symptoms.

Why this particular infection was so refractory to penicillin has not yet been determined since the organism was not fully identified, nor was its penicillin sensitivity studied when first isolated. At present, blood cultures are negative, and these studies cannot be made. If these investigations were made routinely at the outset in every case, information would be on hand to help explain such resistant infections. Plans are being made to administer massive doses of penicillin combined with fever therapy to this patient over a prolonged period.

CASE 9 A 40-year-old executive entered the hospital on February 23, 1944. He complained of lack of energy, occasional vomiting, a weight loss of 30 pounds and intermittent elevations of temperature to 101°F during the previous 4 months.

Physical examination revealed a systolic murmur at the apex and a to-and-fro murmur at the aortic area. The blood pressure was 130/60. The temperature was 100°F. Early clubbing of the fingers was present. A blood culture grew one or two colonies of *Str. viridans* per cubic centimeter of blood. The urine showed a trace of albumin, and the sediment contained occasional casts and white cells. Examination of the blood was negative, the blood sedimentation rate was 79 mm in 1 hour. Agglutination tests for typhoid and Brucella infections were negative. An electrocardiogram showed only left-axis deviation. X-ray studies showed prominence of the heart to the left, apical infection of several teeth and normal sinuses and lungs.

Bacterial endocarditis was diagnosed and 12 gm of sulfadiazine was given daily for 9 days in combination with four hours of artificial fever from typhoid vaccine. Three subsequent blood cultures were sterile. Tonsillectomy and extraction of the infected teeth were done, and the patient was discharged on April 8.

A blood culture taken on the day of discharge later showed five or six colonies of *Str. viridans*, and the patient was advised to take 4 gm of sulfadiazine daily under the supervision of his physician since no penicillin was available. Two blood cultures during May were positive.

The patient was readmitted to the hospital on June 15 and given 100,000 units of penicillin intravenously daily for 10 days and 200,000 units intramuscularly for 5 days. Soon after

discharge his physician gave him another 1,000,000 units intramuscularly.

He remained well. No evidence of infection was found when he was again hospitalized 5 months later for study. As an added precaution he was given 12,500 units of penicillin intramuscularly every 3 hours for 10 days. Twenty-two months after the original penicillin treatment, his condition was still satisfactory.

The rate of progression of cardiac damage is not predictable in bacterial endocarditis. In Cases 1, 4 and 7 valvular or myocardial injury rapidly led to heart failure, whereas in Case 9 no further cardiac damage was apparent even after nine months of infection.

* * *

As demonstrated in Table 1, there was bacteriologic arrest in 7 cases and persistence of infection in 2. Of the former, 4 patients are living and well twenty-four, twenty-three, twenty-two and ten months later, respectively, and 3 died with no signs of bacterial infection. Two died from congestive heart failure, and 1 from rupture of an aortic-valve cusp. In all fatal cases repeated blood cultures before death were sterile. Autopsy was performed in 2 cases, and no organisms were demonstrated. Since it has been shown that relapses usually occur within thirty days of cessation of treatment and are rare after fifty days,⁷ we consider ourselves justified in regarding the surviving patients as cured. Of the bacteriologic failures, one was due to *Br. abortus*, and the other to unknown factors.

Dental sepsis was present in 3 patients. There was none in 2, and in 4 the condition of the teeth was not stated. Infected teeth have long been suspected of being a portal of infection in bacterial endocarditis. Transient bacteremia followed tooth extraction in 75 per cent of 40 persons with marked pyorrhea and in 34 per cent of 38 persons with no dental infection.⁸ Also, a number of cases have been recorded in which tooth extraction seemed to cause the bacterial endocarditis.⁹ On the other hand, dental sepsis has been secondary to emboli lodging in the dentine cavity,⁹ so that the role of dental infection in bacterial endocarditis is difficult to evaluate.

Other portals of infection frequently mentioned are the sinuses and gastrointestinal tract. We have seen no suggestion that the genitourinary tract is also a site for the invasion of organisms in bacterial endocarditis. In 4 cases pyuria was present, and there is a patient in the hospital who had a history of pyuria for four years and developed enterococcal endocarditis following resection of a contracted bladder outlet.

The sedimentation rate of the blood was abnormally high in all cases in which it was determined. In Case 5 it was increased to 54 mm in 1 hour a week after the administration of penicillin had been stopped and cure established. Others have found the sedimentation rate to remain elevated for

It is noteworthy that the diagnosis was made early in this case. Although only moderate doses of penicillin over a relatively short time were used, the patient remained cured twenty-three months later. It is doubtful that the subsequent courses of penicillin were needed, since at no time was there any sign of recurrence. An interesting observation is the occurrence of urticaria shortly after the first course of penicillin, and its disappearance soon after institution of the second course. That the sedimentation rate of the blood does not determine cure is shown by its elevation even after cure had been established. Goerner, Geiger and Blake⁶ have reported its persistent elevation in some cases for more than six weeks.

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The patient was given 20,000 to 30,000 units of penicillin intramuscularly every 2 hours, and 2,420,000 units was administered during the next 32 days. The temperature varied from 99 to 103.6°F, and the urine continued to show blood cells and casts. The white-cell count remained between 10,000 and 20,000. The heart sounds remained normal until January 6, when a systolic murmur and thrill were found in the aortic area, and a diastolic murmur over the entire precordium. Three days later the patient developed acute pulmonary edema, which responded to atropine. On January 20 a pericardial friction rub was heard, 2 days later he developed pulmonary edema and died.

Autopsy The significant findings included subacute bacterial endocarditis of the aortic valve, cardiac hypertrophy and dilatation, serofibrinous pericarditis, a recent splenic infarction, acute glomerular nephritis and congestive heart failure. Microscopical examination of firm, white nodules from the aortic valve showed fibrosis, hyalinization and infiltration by leukocytes, with a predominance of polymorphonuclear cells.

The custom of calling bacterial endocarditis acute if it has been present for less than six weeks and subacute after it has persisted six weeks or longer has less significance than heretofore. In cases that would formerly have been called subacute, penicillin often arrests the illness before it has lasted six weeks, and may prolong the course of the acute type beyond this period. A better way of classifying bacterial endocarditis is by indication of the causative organism, as in pneumonia. This case exemplifies the difficulty of distinguishing acute from subacute disease, since the clinicians considered it acute whereas the pathologists thought it subacute. We have preferred to classify it as bacterial endocarditis due to *Staph aureus*.

CASE 8 A 28-year-old housewife entered the hospital on October 10, 1945. She had had rheumatic fever in childhood and again at the age of 22. Seventeen months before admission, she had had a sore throat and cystitis, both of which had responded rapidly to sulfonamide therapy, but malaise and a low-grade fever had continued. In August there were migratory joint pains and petechiae. Repeated blood cultures were positive for *Sir viridans*. Penicillin, heparin and sulfadiazine were administered unsuccessfully, and for 10 months the patient gave herself 15,000 units of penicillin intramuscularly every 3 hours day and night. In March a sharp pain in the left lumbar region was diagnosed as renal infarction, and in May a chest pain was called pulmonary embolism. Blood cultures remained positive, but she felt well and for 2 months before admission remained afebrile. On the day before entry she experienced a severe bilateral headache with nausea and vomiting. Cerebral embolism was suspected.

Physical examination disclosed a well nourished woman whose weight had been increasing slightly and who did not appear acutely ill. Significant findings were a temperature of 101°F, cardiac enlargement, an apical systolic murmur widely transmitted, a diastolic murmur over the left 3rd and 4th costochondral junctions and *Sir viridans* on blood culture. There were no petechiae, finger clubbing or splenic enlargement. A spinal puncture demonstrated normal dynamics of the fluid, with 297 polymorphonuclear leukocytes per cubic millimeter, a culture of the fluid was sterile. The headache disappeared after this examination, and later specimens of spinal fluid showed no leukocytosis.

Urinalyses showed a trace of albumin, and hemograms, a mild hypochromic anemia, a blood Hinton test was negative. The blood sugar and nonprotein nitrogen determinations were normal.

Three hundred thousand units of penicillin was given by constant intravenous drip daily for 6 days, 200,000 units for 2 days, and 320,000 units for 2 days. A sulfadiazine blood level of 9.1 mg per 100 cc was maintained for 12 days. On discharge the patient was instructed to take 15,000 units of penicillin intramuscularly every 3 hours.

One week later two or three colonies of *Str. viridans* per cubic centimeter of blood were found, and an additional 25,000 units of oral penicillin every 3 hours was prescribed. A few days later the temperature rose to 100.8°F and there were fresh petechiae, so that 1 gm of sulfadiazine every 4 hours was added.

The patient re-entered the hospital on November 21, and was given 500,000 units of penicillin daily by constant intravenous drip for the next 5 weeks. Three blood cultures were negative before discharge on December 28. She continued to give herself 25,000 units of penicillin intramuscularly every 3 hours. Blood cultures remained sterile but the blood sedimentation rate continued to be elevated, and a low-grade fever persisted. On July 10, 1946, when last examined, she had gained 15 pounds in weight and felt well. The blood sedimentation rate was 66 mm in 1 hour. Approximately 100,000,000 units of penicillin had been given during the previous 19 months.

Therapy with relatively large doses of penicillin for five weeks and with moderate doses for seventeen months failed to bring about a cure, although such treatment suppressed the infection and prevented symptoms.

Why this particular infection was so refractory to penicillin has not yet been determined since the organism was not fully identified, nor was its penicillin sensitivity studied when first isolated. At present, blood cultures are negative, and these studies cannot be made. If these investigations were made routinely at the outset in every case, information would be on hand to help explain such resistant infections. Plans are being made to administer massive doses of penicillin combined with fever therapy to this patient over a prolonged period.

Case 9. A 40-year-old executive entered the hospital on February 23, 1944. He complained of lack of energy, occasional vomiting, a weight loss of 30 pounds and intermittent elevations of temperature to 101°F during the previous 4 months.

Physical examination revealed a systolic murmur at the apex and a to-and-fro murmur at the aortic area. The blood pressure was 130/60. The temperature was 100°F. Early doubling of the fingers was present. A blood culture grew one or two colonies of *Str. viridans* per cubic centimeter of blood. The urine showed a trace of albumin, and the sediment contained occasional casts and white cells. Examination of the blood was negative, the blood sedimentation rate was 79 mm in 1 hour. Agglutination tests for typhoid and Brucella infections were negative. An electrocardiogram showed only left-axis deviation. X-ray studies showed prominence of the heart to the left, apical infection of several teeth and normal sinuses and lungs.

Bacterial endocarditis was diagnosed and 12 gm of sulfadiazine was given daily for 9 days in combination with four bouts of artificial fever from typhoid vaccine. Three subsequent blood cultures were sterile. Tonsillectomy and extraction of the infected teeth were done, and the patient was discharged on April 8.

A blood culture taken on the day of discharge later showed five or six colonies of *Str. viridans*, and the patient was advised to take 4 gm of sulfadiazine daily under the supervision of his physician since no penicillin was available. Two blood cultures during May were positive.

The patient was readmitted to the hospital on June 15 and given 100,000 units of penicillin intravenously daily for 10 days and 200,000 units intramuscularly for 5 days. Soon after

discharge his physician gave him another 1,000,000 units intramuscularly.

He remained well. No evidence of infection was found when he was again hospitalized 5 months later for study. As an added precaution he was given 12,500 units of penicillin intramuscularly every 3 hours for 10 days. Twenty-two months after the original penicillin treatment, his condition was still satisfactory.

The rate of progression of cardiac damage is not predictable in bacterial endocarditis. In Cases 1, 4 and 7 valvular or myocardial injury rapidly led to heart failure, whereas in Case 9 no further cardiac damage was apparent even after nine months of infection.

* * *

As demonstrated in Table 1, there was bacteriologic arrest in 7 cases and persistence of infection in 2. Of the former, 4 patients are living and well twenty-four, twenty-three, twenty-two and ten months later, respectively, and 3 died with no signs of bacterial infection. Two died from congestive heart failure, and 1 from rupture of an aortic-valve cusp. In all fatal cases repeated blood cultures before death were sterile. Autopsy was performed in 2 cases, and no organisms were demonstrated. Since it has been shown that relapses usually occur within thirty days of cessation of treatment and are rare after fifty days,⁷ we consider ourselves justified in regarding the surviving patients as cured. Of the bacteriologic failures, one was due to *Br. abortus*, and the other to unknown factors.

Dental sepsis was present in 3 patients. There was none in 2, and in 4 the condition of the teeth was not stated. Infected teeth have long been suspected of being a portal of infection in bacterial endocarditis. Transient bacteremia followed tooth extraction in 75 per cent of 40 persons with marked pyorrhea and in 34 per cent of 38 persons with no dental infection.⁸ Also, a number of cases have been recorded in which tooth extraction seemed to cause the bacterial endocarditis.⁹ On the other hand, dental sepsis has been secondary to emboli lodging in the dentine cavity,⁹ so that the role of dental infection in bacterial endocarditis is difficult to evaluate.

Other portals of infection frequently mentioned are the sinuses and gastrointestinal tract. We have seen no suggestion that the genitourinary tract is also a site for the invasion of organisms in bacterial endocarditis. In 4 cases pyuria was present, and there is a patient in the hospital who had a history of pyuria for four years and developed enterococcal endocarditis following resection of a contracted bladder outlet.

The sedimentation rate of the blood was abnormally high in all cases in which it was determined. In Case 5 it was increased to 54 mm in 1 hour a week after the administration of penicillin had been stopped and cure established. Others have found the sedimentation rate to remain elevated for

six weeks or longer after cure,⁶ and hence it is of no value as a guide for treatment or cure

Sterilization of the blood can be accomplished in the majority of patients with penicillin-sensitive organisms, but not in all. Geiger and Goerner¹⁰ recently reported a case in which infection persisted in spite of a sensitive organism, adequate penicillin, splenectomy and extraction of infected teeth. Other causes for failure in the treatment of bacterial endocarditis are complications from emboli or from the

rheumatic heart disease and 8 per cent with congenital heart lesions develop bacterial endocarditis.

Bacterial invasion of the blood stream is especially likely if a patient with a heart murmur complains of malaise, anorexia, weight loss or fever and if the sedimentation rate of the blood is elevated. We have encountered no case of bacterial endocarditis either in our series or in reviewing the recent literature — in which there was not an elevated sedimentation rate. The routine use of this test in

TABLE 1 Summary of Data in 9 Cases of Bacterial Endocarditis

CASE No	APPROXIMATE DURATION OF DISEASE BEFORE DIAGNOSIS mo	ORGANISM ISOLATED	THERAPY	REMARKS
1	6	<i>Str. viridans</i>	25 000 units of penicillin intramuscularly every 3 hr for 1 day 50 000 units of penicillin intramuscularly every 3 hr for 6 days 100 000 units of penicillin intramuscularly every 3 hr for 7 days 100 000 units of penicillin intramuscularly every 2 hr for 10 days	Patient died of heart failure. Cultures negative for 3 weeks before death.
2	16	<i>Br. abortus</i>	35 000 units of penicillin intramuscularly every 3 hr for 7 days 400 000 units of penicillin intravenously every day for 19 days Sulfadiazine blood level of 6.0–17.5 mg. per 100 cc. for 10 days Sulfamerazine blood level of 11.2–15.8 mg. per 100 cc. for 12 days	Case considered a therapeutic failure.
3	1½	<i>Str. viridans</i>	25 000 units of penicillin intramuscularly every 3 hr for 7 days 40 000 units of penicillin intramuscularly every 3 hr for 21 days Total of 4,000 000 units of penicillin 3 mo. later	Patient well 10 mo. later.
4	5	None*	400 000 units of penicillin intravenously every day for 6 days Dicoumarol for 6 days Sulfadiazine blood level of 12.8–14.8 mg. per 100 cc. for 6 days	Patient died of ruptured aortic valve, blood cultures negative, no evidence of infection at autopsy.
5	2	<i>Str. viridans</i>	160 000 units of penicillin intravenously every day for 7 days 28 000 units of penicillin intramuscularly every 3 hr for 9 days	Patient well 23 mo. later.
6	6	<i>Str. viridans</i>	100 000 units of penicillin intravenously every day for 10 days 12 500 units of penicillin intramuscularly every 3 hr for 10 days 2,000 000 units of penicillin later	Patient well 24 mo. later.
7	1½	<i>Staph. aureus</i> (coagulase positive)	30 000 units of penicillin intramuscularly every 2 hr for 4 days 20 000 units of penicillin intramuscularly every 2 hr for 17 days 30 000 units of penicillin intramuscularly every 2 hr for 11 days	Patient died of heart failure. Blood cultures negative for 3 wk. before death.
8	7	<i>Str. viridans</i>	15 000 units of penicillin intramuscularly every 3 hr for 10 mo. 300 000 units of penicillin intravenously every day for 6 days 200 000 units of penicillin intravenously every day for 2 days 320 000 units of penicillin intravenously every day for 2 days Sulfadiazine blood level of 9.1 mg. per 100 cc. for 12 days 15 000 units of penicillin intramuscularly every 3 hr for 14 days 25 000 units of penicillin orally every 3 hr for 7 days 500 000 units of penicillin intravenously every day for 35 days 25 000 units of penicillin intramuscularly every 3 hr for 7 mo.	Blood cultures negative, but signs of infection persist.
9	9	<i>Str. viridans</i>	100 000 units of penicillin intravenously every day for 10 days 25 000 units of penicillin intramuscularly every 3 hr for 5 days 1 000 000 units of penicillin later	Patient well for 22 mo.

*Diagnosis made on basis of clinical findings.

underlying heart disease, such as congestive heart failure, rupture of valve leaflets, perforation of the heart wall with cardiac tamponade, rupture of mycotic aneurysms or coronary occlusion, and from rupture of the spleen, massive pulmonary hemorrhage, focal nephritis with uremia, toxemia, cerebral embolism, reinfection with penicillin-resistant organisms and unrelated diseases.

Early Diagnosis

Owing to delay in diagnosis the organism becomes more firmly entrenched in a network of fibrin, with extension of damage to the heart valves, increased toxemia and complications from emboli. Such delay is frequent; it is not unusual for mild symptoms to be present for months before the diagnosis is even suspected. As many as 5 per cent of patients with

examination of patients with heart murmurs would be of value in selecting those needing further investigation. If patients with heart murmurs recorded their temperatures three times a day for one or two weeks whenever they noticed a change in their state of health, earlier suspicion would be aroused, leading to prompt study. A special search should be made for petechiae, Osler nodes, Janeway lesions, splinter hemorrhages beneath the nail bases, glossiness of the rim of the skin at the nail bases, indicative of early clubbing of the fingers,¹¹ splenomegaly and changes in the heart murmur. The rarity of bacterial endocarditis with auricular fibrillation is often mentioned as being of diagnostic value. In 286 cases of auricular fibrillation, however, it was found in 12.5 per cent,¹² so that

possibility of bacterial endocarditis must not be too readily dismissed because the heart is fibrillating

Bacteriologic Considerations

Streptococci belonging to the alpha-hemolytic group cause approximately 90 per cent of cases of bacterial endocarditis. Other organisms that have been found responsible include *Neisseria sicca*, *N. catarrhalis*, *N. gonorrhoeae*, *N. intracellularis*, *N. farosa*, *Diplococcus mucosus*, *D. crassus*, *Micrococcus ananrus*, *Gaffkyia tetragena*, *Staph. albus*, *Staph. aureus*, *Corynebacterium*, *Br. suis*, *Br. abortus*, *Br. melitensis*, *Spirillum surati*, *Streptobacillus moniliformis*, *Actinomyces necrophorus*, *Bacillus döderleinii*, *Haemophilus influenzae*, anaerobic hemolytic streptococci, enterococci, pneumococci and fungi such as *Monilia*, *Erysipelothrix*, *Leptothrix* and *Histoplasma*.

Str. viridans is often discussed as if it were an individual organism, but this is not so. It is a group of streptococci that produce a green pigment on blood agar, and includes *Str. salivarius*, *Str. equinus*, *Str. bovis* and its varieties and *Str. thermophilus*.¹⁴ Enterococci, notably *Str. faecalis*, may be mistaken for one of the viridans group unless special studies are undertaken. There has recently been reported isolation from cases of bacterial endocarditis of a *Str. viridans* that differs from other members of this group and has been designated by its discoverers *Streptococcus sbe*.¹⁵

It is not possible to compare the clinical course of infection arising from each of these streptococci, since they are rarely identified or reported. That there are differences is shown by the sensitivity to penicillin of some — for example, *Str. salivarius* — and the resistance of others, notably *Str. faecalis* and *Str. mulinaceous* (as in Case 1). With *Str. sbe*, the outlook is grave.¹⁵ The origin of the infection may be suggested by full identification, for some species inhabit the mouth, and some the intestinal tract, and others occur in animals or in milk products.

In obtaining blood for culture, at least 20 cc should be withdrawn, preferably following a chill when the fever is mounting. Pour plates are usually made with 0.5 cc., 1 cc. and 3 cc. of blood, and the rest is divided between two flasks, each containing at least 75 cc. of broth. Enriched mediums, such as hormone broth, heart-brain broth and tryptose-phosphate broth, are preferable since fastidious organisms, as well as others, will grow in them. Growth may be delayed, so that cultures should be incubated for at least ten days before being discarded. Repeated cultures are often necessary before the organism is isolated, for the bacteria may be present only intermittently in the blood stream. Para-aminobenzoic acid to neutralize sulfonamides and clarase to neutralize penicillin are sometimes added to the culture mediums, but in most cases the diluting effect of relatively large amounts of medium

is sufficient. If unusual infections are to be recognized, special bacteriologic examinations are necessary. In obscure cases, anaerobic cultural methods and special mediums, such as Sabouraud's medium, are required. Libman¹⁶ believes that positive cultures can be obtained in 84 to 95 per cent of cases, and in 1912 demonstrated organisms in the blood stream in 75 of 75 patients with bacterial endocarditis.

Treatment

Few investigators agree on optimal methods of treatment with penicillin. Differences of opinion exist regarding proper dosage, manner of administration, duration of therapy and use of anticoagulants, but almost all agree that the dose should be large and its administration prolonged. Some workers recommend an arbitrary dose of 500,000 units daily for five weeks.^{7, 17} Others individualize therapy, giving sufficient penicillin to raise the blood level five to ten times higher than that needed to inhibit growth of the organism.^{1, 18} The latter method is preferable, since organisms vary in their sensitivity to penicillin, and different blood levels are obtained from given amounts of penicillin. It may be necessary to give as much as 5,000,000 units daily, as in a patient now under treatment, to obtain effective concentrations in the blood. Increased penicillin resistance of the organism, although rare,¹⁹ may occur and remain undetected unless repeated sensitivity tests are done.

Administration by constant intravenous drip is generally considered superior to other methods, since higher and more constant blood levels are obtained.¹ Intermittent intramuscular injection is frequently employed. There does not appear to be any significant difference in the percentage of cures by either method if sufficient penicillin is used.

Anticoagulant therapy is not generally used in conjunction with penicillin, since complications are frequent and the end results do not appear to be improved. For patients who do not respond to penicillin, however, it may have a place. Loewe¹ reported 2 cases and mentioned 5 others in which the combined treatment was required to achieve cure.

Bacteriophage was found by MacNeal²⁰ to contribute to the cure of a patient with enterococcal endocarditis. In view of the poor prognosis in this type of infection, further trials with bacteriophage are warranted. Surgery has become increasingly important in treating bacterial endocarditis not only for eliminating foci of infection but also for correcting congenital cardiac anomalies. To our knowledge, no one has reported the use of artificial fever as an adjunct to penicillin therapy of bacterial endocarditis. Its possible value is suggested by the improvement in results with the sulfonamides when fever therapy was added.¹⁸

Congestive heart failure may occur during the treatment of bacterial endocarditis, and measures

to forestall this complication should be instituted. Frequently, the patient should be digitalized, activity markedly restricted, and sodium prohibited. Five per cent glucose in distilled water, rather than physiologic saline solution, should be used for the intravenous administration of penicillin. The amount of sodium in sodium penicillin need not be considered, for in 1,000,000 units there is approximately 167 mg of the sodium ion, equivalent to the amount in about 20 cc of physiologic saline solution.²¹

SUMMARY

Nine cases of bacterial endocarditis are reported in which penicillin failed to sterilize the blood stream in only 2.

Earlier diagnosis would be possible if the presence of bacterial infection were questioned in all patients with heart murmurs, if such patients were instructed to record their temperatures whenever a change in health occurred and if the blood sedimentation rate were determined routinely at examinations. A plea is made for more detailed bacteriologic study of causative organisms, and especially for the identification of alpha-hemolytic streptococci.

Treatment may be carried out with arbitrary doses of penicillin, but basing doses on penicillin sensitivity studies and determinations of blood levels ensures the administration of adequate amounts. Five weeks of therapy is generally considered satisfactory. Therapeutic failure is more frequently the result of complications from the underlying heart disease than of the infection, therefore, the

importance of early diagnosis, before complications arise, is emphasized.

REFERENCES

1. Loewe, L. Combined use of anti-infectives and anticoagulants in treatment of subacute bacterial endocarditis. *Bull. New York Acad. Med.* 21: 59-86, 1945.
2. Herrell, W. E. and Nichols, D. R. Clinical use of streptomycin: report of forty-five cases. *Proc. Staff Meet., Mayo Clin.* 20: 449-462, 1945.
3. Abbott, M. E. *Atlas of Congenital Cardiac Disease*. 62 pp. New York: American Heart Association, 1936.
4. Gross, R. E. Complete surgical division of patent ductus arteriosus: report of 14 successful cases. *Surg. Gynec. & Obst.* 78: 36-43, 1944.
5. Barbagallo, G. La sterno-medullo-cultura nelle malattie infettive. *Polisclnico (sez. med.)* 45: 230-243, 1938.
6. Goerner, J. R., Geiger, A. J. and Blake, F. G. Treatment of subacute bacterial endocarditis with penicillin: report of cases treated without anticoagulant agents. *Ann. Int. Med.* 23: 491-519, 1945.
7. Christie, R. V. Penicillin in subacute bacterial endocarditis: report to Medical Research Council on 147 patients treated in 14 centres appointed by Penicillin Clinical Trials Committee. *Brit. Med. J.* 1: 381-383, 1946.
8. Okell, C. C. and Elliott, S. D. Bacteraemia and oral sepsis, with special reference to aetiology of subacute endocarditis. *Lancet* 2: 869-872, 1935.
9. Barnfield, W. F. Subacute bacterial endocarditis and dental procedures. *Am. J. Orthodontics (Oral Surg. Sect.)* 31: 55-58, 1945.
10. Geiger, A. J. and Goerner, J. R. Benzyl penicillin failure to sterilize blood in subacute bacterial endocarditis. *Yale J. Biol. & Med.* 18: 377-380, 1946.
11. White, P. D. *Heart Disease*. Third edition. 1025 pp. New York: Macmillan Co., 1944.
12. Hurxthal, L. M. Clinical observations on subacute bacterial endocarditis. *Boston M. & S. J.* 197: 41-46, 1927.
13. McDonald, R. K. Coincidence of auricular fibrillation and bacterial endocarditis. *Am. Heart J.* 31: 308-313, 1946.
14. Sherman, J. M. Streptococci. *Bact. Rev.* 1: 3-97, 1937.
15. Loewe, L., Plummer, N., Niven, C. F. Jr., and Sherman, J. M. Streptococcus *s. b.* in subacute bacterial endocarditis. *J. A. M. A.* 130: 257, 1946.
16. Lubman, E. and Friedberg, C. K. *Subacute Bacterial Endocarditis*. Edited by H. A. Christian. 108 pp. New York: Oxford University Press, 1941.
17. Flippin, H. F., Mayock, R. L., Murphy, F. D., and Wolferth, C. C. Penicillin in treatment of subacute bacterial endocarditis: preliminary report on twenty cases treated over one year ago. *J. A. M. A.* 129: 841-843, 1945.
18. Favour, C. B., Janeway, C. A., Gibson, J. G., II, and Levine, S. A. Progress in treatment of subacute bacterial endocarditis. *New Eng. J. Med.* 234: 71-77, 1946.
19. Editorial. Dosage of penicillin. *New Eng. J. Med.* 234: 706-708, 1946.
20. MacNeal, W. J., Blevins, A., and Poindexter, C. A. Clinical arrest in enterococcal endocarditis. *Am. J. M. Sc.* 211: 40-50, 1946.
21. Gibson, A. Personal communication.

PERSISTENCE OF REMISSIONS OF THYROTOXICOSIS AFTER CESSATION OF THIOURACIL THERAPY*

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THE great effectiveness of thiouracil and related compounds in controlling thyrotoxicosis has been well established. In most cases this type of therapy can be continued for many months or years without the production of ill effects or a state of refractoriness. One cannot be certain, however, that undesirable metabolic abnormalities will not develop after long intervals of therapy. For this reason, as well as others, it is important to determine the optimal treatment necessary to produce remissions that will be sustained after cessation of thiouracil therapy. Only a few results dealing with this subject have been reported.¹⁻⁷ Approximately a year ago it was found that of 100 patients with thyrotoxicosis treated with thiouracil, 49 were in a remission for intervals of three to twenty-one months following the discontinuance of treatment.⁶ These studies have been extended and are the basis of this report.

The types of cases treated, the outline of therapy and the nature of the follow-up examinations have previously been presented.⁶ So far as the selection of cases for treatment without thyroidectomy is concerned, the only factor that appears to be significant is that few patients with thyroid glands more than five times the normal size were treated.

This report presents the results in all patients who had a cessation in thiouracil therapy, including the cases in which the patient stopped treatment of his own accord. Seven patients disappeared from the clinic during their second or third course of therapy and were not heard from in spite of repeated solicitations. All of these are included in the group experiencing relapses of the disease, but it is possible that some of them are now in remission. Several of the other patients, especially the ones with sustained remissions, would probably have disappeared from observation had it not been for special requests for their return.

On cessation of thiouracil therapy the patients were given a clinical examination and a test of basal metabolic rate at monthly intervals for four months, bimonthly until the end of a year and then at intervals of from three to six months.

Of the 111 patients who were treated with thiouracil or one of its derivatives and had a discontinuation of therapy, 47 have had no evidence of re-appearance of thyrotoxicosis, although they have not received any treatment for intervals of from three to thirty-one months. In addition, 4 patients, after receiving a second course of thiouracil therapy, have experienced a sustained remission for intervals of from five to thirteen months. Thus, 51 of the 111 patients, or 46 per cent, appear to need no more treatment. Indeed, 44 have been free of thyrotoxicosis for more than a year after cessation of therapy, and 33 have remained well for more than eighteen months (Fig 1). Moreover, of the patients who have been well for more than a year without treatment, only 1 has had a relapse of the thyrotoxicosis. Most of the patients who had a relapse had it within a few months. 70 per cent had it within two months, and 88 per cent within five months. One patient, however, had a relapse after having been well for thirteen months without treatment.

Many of the patients who experienced relapses were treated again with thiouracil. Of 12 who have again had a cessation of therapy 4 have had a persistent remission, but 8 have had another relapse. Four of the 8 patients, however, were treated for less than six months in the second course of therapy.

Only 4 of 21 male patients, or 18 per cent, had a sustained remission, whereas 47 of 90 female patients, or 52 per cent, remained well. Those experiencing a decrease in the size of the thyroid gland while receiving thiouracil treatment were more prone to have a sustained remission of the disease than the ones whose glands increased in size or showed no change. Patients with small goiters or slight thyrotoxicosis experienced a more persistent response than the ones with large goiters or severe thyrotoxicosis. Factors that did not seem to be of much significance in obtaining a persistent remission were the age of the patient, the duration of the disease and the nodularity of the thyroid gland. The duration of therapy was of distinct significance, but varied a great deal in different cases. In fact, none of the 3 patients treated continuously for the longest interval remained well (Fig 2).

In a consideration of the correlation of the duration of treatment with sustained remissions of

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thyrotoxicosis that were obtained, it is to be borne in mind that the prolonged course of therapy in some cases was due to the suggestion by the clinical course of the patient that a relapse would probably result if the therapy were discontinued. The deci-

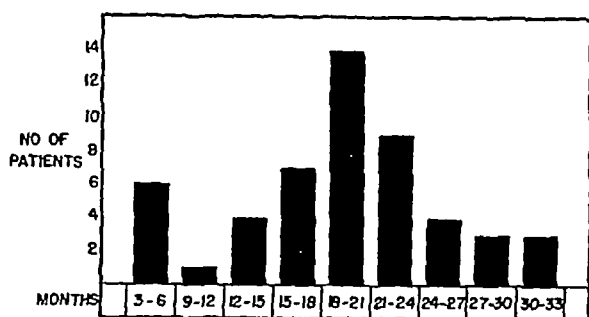


FIGURE 1 Duration of Sustained Remissions

All the patients included in this chart are in a state of euthyroidism at present. Thus far, none of our patients, except one who has been free of thyrotoxicosis for a year, have had a re-appearance of this disease.

sion regarding when treatment was to be discontinued was, in part, based on the maintenance dose of thiouracil that was required.

Nine patients were treated with thiouracil during pregnancy for a month or longer. Three were treated for several months before fertilization, with continued therapy throughout pregnancy. The thyrotoxicosis was well controlled. No infants were found to have a goiter or a disturbance in thyroid function at birth or during the interval of more than a year that they have been followed.

Of 9 female patients with malignant exophthalmos, 5 have had a remission that has persisted after cessation of therapy. None of the 4 male patients with this disturbance, however, have remained well.

In none of the more than 300 patients that we have treated with thiouracil or one of its derivatives has carcinoma of the thyroid gland been found, although some patients have received one of these drugs most of the time for three years. Moreover, in the majority of cases treated for eight months or longer, the thyroid gland was found to have decreased in size or not to have shown any essential change.

No untoward effects, other than the types of toxic reactions that have been observed with short intervals of thiouracil therapy, have been demonstrated in the patients given this compound for a year or longer. Such complications, however, must continue to be considered.

The following brief résumés of some of the case reports are presented to indicate the nature of the problems and the results obtained.

Cases with Persistent Remissions

CASE 21 A 36-year-old Negress, during the 13 months before admission, had observed nervousness, hyperhidrosis, heat intolerance, weakness, fatigue, goiter, hyperorexia, a loss of 35 pounds in weight, palpitation, dyspnea and slight

exophthalmos. Physical examination revealed a moist, hot skin, a tremor, a pulse rate of 120, slight exophthalmos, diffuse enlargement of the thyroid gland to approximately two and a half times the normal size and a loud bruit. The basal metabolic rate was above +80 per cent on two occasions, and the protein-bound iodine was 14 microgm per 100 cc of plasma. With no treatment other than thiouracil, the basal metabolic rate became normal within 2 months and has subsequently remained normal for 32 months, although no treatment has been given for the last 17 months. The patient regained all the weight that she lost and has felt well in every way.

CASE 31 A 32-year-old Negress stated that for 5 months before hospitalization she had been bothered by nervousness, weakness, fatigue, hyperorexia followed by anorexia, diarrhea, a loss of 50 pounds in weight, palpitation, tachycardia, dyspnea, orthopnea, edema of the legs, hyperhidrosis and heat intolerance. Physical examination disclosed congestive heart failure, with a pulse rate of 110, a warm, moist skin, a tremor, marked exophthalmos, nodular enlargement of the thyroid gland to three times the normal size and a loud bruit. The basal metabolic rate was +64 per cent, but 1 month after the beginning of thiouracil therapy it was normal. This drug was given continuously for 18 months, during the last 9 of which the patient was pregnant, giving birth to healthy twins. The dosage of thiouracil during the last

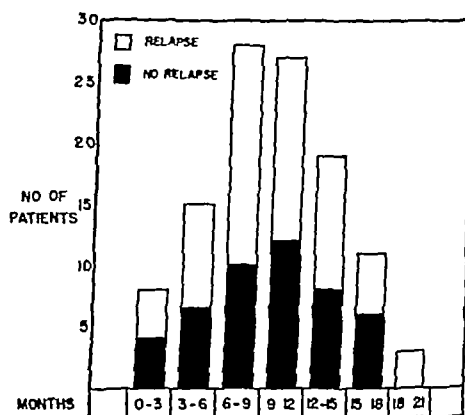


FIGURE 2 Interval of Continuous Treatment

The percentage of sustained remissions does not appear to be particularly affected by the duration of therapy. In some cases, however, the duration of the therapy was governed by the response of the patients while they were receiving thiouracil.

5 months of pregnancy was 0.2 gm daily. Although therapy has been discontinued for 18 months, the patient has remained in excellent condition. She has gained a total of 85 pounds, and the thyroid gland seems to be normal in size, shape and consistency.

CASE 77 A 35-year-old woman had had moderately severe thyrotoxicosis of 5 months' duration, malignant exophthalmos, diffuse enlargement of the thyroid gland to approximately one and three quarter times the normal size and elevation of the basal metabolic rate to +55 per cent. The response of the thyrotoxicosis to thiouracil was slow, no more than 0.4 gm daily of this compound was used because of the malignant exophthalmos. In spite of this precaution, the ophthalmopathy became worse, so that treatment with desiccated thyroid was begun. Thereafter, the eyes and the thyrotoxicosis showed slow improvement. Thiouracil was given for 11 months and was then discontinued, as was the desiccated thyroid. The patient has been free of hyperthyroidism for 18 months subsequently, and during this interval she went through a normal pregnancy. The exophthalmos has improved slightly.

CASE 99 The patient was a 51-year-old unmarried woman who had moderately severe thyrotoxicosis that had begun 2 months before treatment with thiouracil. The basal metabolic rate decreased from +62 per cent to -9 per cent after treatment for 5 weeks. Therapy was continued for 11 months

The patient has remained in excellent condition in spite of the cessation of treatment 18 months ago. The thyroid gland, which was two and a half times the normal size before treatment, is about one and three quarters times normal.

Case 154. A 28-year-old Finnish woman had had thyrotoxicosis for 1 year. The lowest basal metabolic rate preceding treatment had been +51 per cent, and the rate became normal within 4 weeks after thiouracil therapy was started. The treatment was continued for only 6 months, but the patient has remained entirely well for 21 months subsequently. During that time she has gone through a normal pregnancy. The thyroid gland, which was estimated to be one and three quarters times the normal size before therapy, seems to be normal in every respect.

Case 178. A 63-year-old woman with thyrotoxicosis of 3 months' duration was found to have a basal metabolic rate of +47 per cent. Within 4 months of treatment with thiouracil, the metabolic rate was normal. This therapy was given for a total of 8 months and was discontinued, but the patient has remained well for 14 months subsequently. The thyroid gland, which was about one and a third times the normal size before treatment, is normal.

Cases with Relapses

Case 2. A 55-year-old painter had had symptoms of thyrotoxicosis for 1 year. The disease was severe and was associated with heart failure and malignant exophthalmos. The thyroid gland was about three times the normal size. The basal metabolic rate was +84 per cent. Within 4 weeks after thiouracil therapy was started, the basal metabolic rate was normal. After treatment was given for 5 months, the patient failed to return to the clinic, in spite of repeated requests. Seven months later, he returned in a condition that was almost as poor as that at the beginning of treatment. With thiouracil therapy, the basal metabolic rate became normal after 10 weeks. This course of treatment was continued for 10 months, but the patient had a relapse 1 month thereafter. A third course of thiouracil therapy was started, but the patient disappeared after it had been given for 2 months.

Case 4. A 49-year-old female factory worker had had thyrotoxicosis for 22 years. During the early phase of the illness she had been subjected to three thyroid operations. She had taken Lugol's solution periodically for 22 years. The basal metabolic rate was +56 per cent, and the thyroid gland was about two and a half times the normal size. She showed an adequate response to thiouracil, but this therapy was given continuously for 20 months. She remained in excellent condition for 4 months after cessation of therapy but developed a relapse during the subsequent month. Potassium iodide did not cause a complete response. Thiouracil, in amounts of 0.2 gm daily, was then given, but the patient developed agranulocytosis. Thereafter she was treated satisfactorily with radioactive iodine.

Case 5.* A 35-year-old housewife had had mild thyrotoxicosis for 1 year. The basal metabolic rate was +45 per cent, and the thyroid gland was two and a half times the normal size. The disease was readily controlled with thiouracil, and the basal metabolic rate finally decreased to -25 per cent under a maintenance dose of 0.1 gm every 2 days. This therapy was given for 11 months and then discontinued. The patient, however, had a relapse 6 weeks later. On resumption of thiouracil therapy a febrile reaction occurred, a similar reaction followed tetramethylthiourea. Potassium iodide was then given, but within 3 days a violent bullous eruption developed. This therapy was discontinued, and the patient was then treated satisfactorily with radioactive iodine.

Case 14. A 52-year-old railroad fireman with severe thyrotoxicosis of 3 months' duration had a thyroid gland that was three times the normal size and a basal metabolic rate of +64 per cent. He showed a standard response to treatment with thiouracil, the dosage in this case was initially about 1 gm. daily, as was that in the other cases at this early stage of development of thiouracil therapy. After the

patient had been treated for 4 months, the thyroid gland had increased to six times the normal size, but with 2000 r of x-ray therapy over the gland, it decreased to its original size. Thiouracil treatment was discontinued after it had been given continuously for 19 months. The patient remained in good condition for 2½ months but then had a relapse. Another remission was readily induced with 6-methylthiouracil and was maintained with potassium iodide, which was given for 4 months. Three months after cessation of this therapy, a relapse occurred. Another remission was produced within 3 weeks, 6-butylthiouracil therapy being employed. Potassium iodide was then used as the only treatment for 6 weeks. A relapse occurred 4 months after the iodide had been stopped. Radioactive iodine is now to be used.

Miscellaneous Cases

One patient has taken thiouracil most of the time for three years. Of her own volition, she stopped the treatment five times, on each occasion she permitted a lapse of about two months without therapy, and each time a relapse occurred within about a month. A patient who had taken thiouracil continuously for eighteen months had a relapse within a month after stopping treatment. A second course of therapy was given for nine months, consisting of thiouracil for the first two months and potassium iodide for the last seven. She has remained in excellent condition for ten months following the cessation of antithyroid treatment. Another patient† received thiouracil for eight months and had a remission that persisted for ten months after therapy had been stopped. She then had a relapse, which was treated for a month with ethyl-diiodobromate⁹, a remission has been present for eight months. Still another patient,† treated with thiouracil for six months, had a remission lasting six months after treatment was stopped. Although a moderately severe relapse occurred, she responded well to para-aminobenzoic acid, obtaining a remission that has lasted for eight months since the cessation of therapy. One patient who was receiving desiccated thyroid for hypometabolism at the time she developed thyrotoxicosis not only had a remission of the Graves's disease that has lasted for twenty-eight months but also again developed hypometabolism with a basal metabolic rate of -27 per cent. One patient has received tetramethylthiourea, thiouracil or propylthiouracil continuously for twenty months, because on the basis of the maintenance doses necessary, it is apparent that a relapse would soon take place if treatment were to be stopped. In another case, in which the course was similar after the administration of thiouracil continuously for a year, radioactive iodine was given, since a sustained remission did not appear promising with thiouracil therapy. In 3 similar cases the thiouracil treatment was discontinued to ascertain whether a remission would result, but in each a relapse developed within a month.

DISCUSSION

The results presented above indicate that thiouracil or related compounds can be used alone in the control of many cases of thyrotoxicosis. This raises the question whether thiouracil derivatives, radioactive iodine or thyroidectomy should be prescribed in most cases of thyrotoxicosis. This query can be better answered when more is learned about the possible ill effects of the newer types of treatment. On the basis of the present results, however, it appears unnecessary to perform a subtotal thyroidectomy in many cases of thyrotoxicosis. In patients with large nodular goiters and those with pronounced compression of the trachea or esophagus, thyroidectomy is indicated, but essentially all the other cases can be treated with antithyroid drugs or radioactive iodine 5-10.

*This case was reported by Chapman and Evans⁸ in 1946 (Case 16).

†These cases are included in the group with relapses and not in that with persistent remissions.

Carcinoma of the thyroid gland occurs so rarely in patients with thyrotoxicosis that the routine removal of the gland as a prophylactic measure does not seem justified.¹¹ There is a possibility that thyroid carcinomas are associated with radioactive iodine or thiouracil therapy, but there is no evidence of such an association.

There is also a possibility that radioactive iodine will produce damaging effects to tissues other than the thyroid gland, especially the kidneys, but no such ill effects have been demonstrated in any patient. The main handicap in depending on radioactive iodine, aside from its scarcity, is in estimating the dosage that is required. Excessive doses may produce myxedema, whereas inadequate amounts may not control the thyrotoxicosis. If the dosage of radioactive iodine is insufficient, however, additional doses can be given, or the patient can be treated with one of the thiouracils.

The newer thiouracils, especially 6-propylthiouracil and 6-cyclopropylthiouracil,^{9, 12} can be used with relative safety, and it seems to be safe to dispense them widely. With this type of therapy the basal metabolic rate can be adjusted to the desired level. Moreover, with increased experience with these compounds, the frequency with which the patients must consult the physician can be greatly reduced. Whether the incidence of remissions will be the same as that with thiouracil is not known, although this appears probable. In most patients with thyrotoxicosis it appears desirable to use propylthiouracil for about nine months, or longer, before any other treatment is given. If a relapse occurs, some of the patients can be treated with radioactive iodine, and the others with additional courses of propylthiouracil.

The duration of continuous thiouracil therapy is important. It is believed that in most cases the drug should be given for nine to fifteen months. This interval is arbitrary in some cases, but in others it is indicated by the clinical course of the patient. Patients who continue to require more than 50 mg of thiouracil daily, those with thyroid glands that enlarge even though no hypothyroidism exists, those with increasing manifestations of malignant exophthalmos and those with a loud bruit over the thyroid gland usually need to be treated for a longer interval. On the other hand, the therapy can be stopped in patients who have been in good condition for several months even with a daily dosage of thiouracil of 50 mg, the ones whose thyroid glands have decreased in size during therapy, those with no bruit over the thyroid gland and those who maintain a normal metabolic rate in spite of distressing situations. The manifestations of thyrotropic activity thus appear to be important aids in regulating the duration of therapy.

No criteria have been found that enable an accurate prediction of just which patients will develop a remission that will persist after cessation

of thiouracil therapy, but a few factors are known to have some influence on the course of the disease. On the basis of the results presented above, it appears that the majority of female patients with small goiters and mild thyrotoxicosis experience a remission of the disease that persists after cessation of thiouracil therapy, the results are not so good if the thyrotoxicosis is severe, if the goiter is large or if the patient is a male. The duration of the disease preceding therapy, the age of the patient and the nodularity of the gland do not appear to influence the incidence of remissions, but as larger series of cases are analyzed and as an opportunity is afforded to control some of the variable characteristics, these factors will probably be found to affect the prognosis.

Contrary to the impression of others,⁷ we do not believe that nodular goiters contraindicate prolonged thiouracil therapy. Moreover, in this clinic, pregnancy has not been a contraindication to thiouracil therapy. In fact, patients who are found to have thyrotoxicosis during pregnancy can possibly be treated more safely with propylthiouracil than with radioactive iodine or by thyroidectomy. It is essential, however, to employ the smallest amount of propylthiouracil that is necessary. For added safety, we have adopted the policy of using small doses of potassium iodide in conjunction with the propylthiouracil. It has been shown that thiouracil enters the blood of rat fetuses,¹³ and that in large doses this compound produces goiter and impairment of growth of the fetuses.¹³⁻¹⁵ Moreover, goiter has been observed at birth in a child,¹⁶ but the dosage of thiouracil was larger than is now known to be necessary. The mother receiving thiouracil probably should not nurse her child, since the concentration of the compound in milk is high.¹⁷

SUMMARY

Of 111 thyrotoxic patients who were treated with thiouracil and had a cessation of therapy, 51 are in remissions that have lasted for three to thirty-one months. Forty-four patients have been free of thyrotoxicosis for more than a year after cessation of therapy, and 33 have remained well for more than eighteen months. Of all the patients who remained well without treatment for more than a year, only 1 had a relapse. Following the cessation of treatment with thiouracil, most of the patients who had a relapse had it within a few months: 70 per cent had it within two months, and 88 per cent within five months.

Factors that tended to favor persistent remissions were as follows: female sex, small goiter and a mild degree of thyrotoxicosis. The age of the patient, the duration of the disease and the nodularity of the thyroid gland were not found to exert a significant influence, but these factors may prove important when larger series of cases are analyzed.

The good effects obtained with thiouracil encourage the frequent use of its less toxic derivative, 6-propylthiouracil, in the treatment of thyrotoxicosis. This therapy, radioactive iodine or a combination of the two appears to offer the most satisfactory method of treating the majority of patients with thyrotoxicosis, but further experiences may reveal complications from these types of treatment that are of greater magnitude than are anticipated at present. Therefore, patients treated by these newer methods must be followed carefully.

REFERENCES

1. Atwood, E. B. Thiouracil treatment in hyperthyroidism. *J Clin Endocrinol* 4:229-245 1944
2. Rose, E., and McConnell J. Thiouracil in treatment of thyrotoxicosis. Clinical experience with 37 cases. *Am J Med Sci* 203:561-576 1944.
3. Williams, R. H. Antithyroid drugs with particular reference to thiouracil. *Arch Int Med* 74:479-487 1944
4. Atwood, E. B. Chemotherapy of hyperthyroidism. *The Harvey Lectures Series* XL, 1944-45. Pp 195-235
5. Barr, D. P. and Shorr, E. Observations on treatment of Graves disease with thiouracil. *Ann Int Med* 23:754-778 1945
6. Williams, R. H. Thiouracil treatment of thyrotoxicosis: results of prolonged treatment. *J Clin Endocrinol* 6:1-22 1946
7. Beierwaltes, W. H. and Sturgis, C. C. Remissions in thyrotoxicosis after thiouracil. *J A M A* 131:755-758 1946
8. Chapman, E. M. and Evans, R. D. Treatment of hyperthyroidism with radioactive iodine. *J A M A* 131:86-91 1946
9. Williams, R. H. Unpublished data.
10. Hertz, S. and Roberts, A. Radioactive iodine in study of thyroid physiology: use of radioactive iodine therapy in hyperthyroidism. *J A M A* 131:81-86 1946
11. Rogers, W. F. Jr. Asper, S. P., Jr., and Williams, R. H. Unpublished data.
12. Atwood, E. B. and Vander Laan, W. P. Thiouracil derivatives of greater activity for treatment of hyperthyroidism. *J Clin Endocrinol* 5:424-430, 1945
13. Williams, R. H. Further studies of absorption, distribution and elimination of thiouracil. *J Clin Endocrinol* 4:385-393, 1944
14. Hughes, A. M. Cretinism in rats induced by thiouracil. *Endocrinology* 34:69-76 1944
15. Goldsmith, E. D. Gordon, A. S. and Chanipper, H. A. Analysis of effects of continued thiouracil treatment in pregnancy and on development of offspring in rat. *Am J Obst & Gynec* 49:197-206, 1945
16. Eaton, J. C. Treatment of thyrotoxicosis with thiouracil. *Lancet* 1:171-174 1945
17. Williams, R. H. Kay, G. A., and Jandorf, B. J. Thiouracil: its absorption, distribution and excretion. *J Clin Investigation* 23:613-627 1944

ACUTE BRUCELLOSIS AMONG LABORATORY WORKERS*

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UNDULANT fever occurs frequently among laboratory workers handling cultures of Brucella organisms.¹ This report is a summary of such infections in 17 persons engaged in investigative work with these organisms. The organization of the laboratories at Camp Detrick made it possible to gather serologic data before infection. These cases offered an unusual opportunity to observe the clinical course of this disease from the onset of illness and to submit several chemotherapeutic agents to clinical trial.

A Brucella vaccine was given to all members of the laboratory group, including the 17 who subsequently contracted brucellosis. Vaccination produced changes in the agglutination reaction and the opsonocytaphagic index, and may have altered the course of illness. This report is not concerned with an evaluation of the prophylactic efficacy of the vaccine.

The patients were all previously healthy young adults who gave no history or laboratory evidence of past Brucella infection. They had been under our direct observation or cognizance for three to fourteen months, the average period being six and a half months. The diagnosis in these patients was based on the clinical course of the disease, the development of high Brucella agglutinin titers and, in most cases, the isolation of the etiologic agent from the blood. Tables 1 and 2 present many of the pertinent data.

*From the Station Hospital, Camp Detrick, Frederick, Maryland.

CLINICAL ASPECTS

Incubation Period

The data are of limited help in determining the incubation period, since all the patients were in almost daily contact with the infecting organism for three to thirteen months before they became ill. The incubation period was known to have been at least four weeks in 1 case, since there had been no opportunity for exposure for that length of time immediately preceding the onset of the illness.

Symptoms

The interval between the appearance of the first prodromal symptoms and the time when illness was well established and incapacitating was less than twenty-four hours in 4 patients. The interval was less than seven days in all patients except one, whose symptoms increased slowly over a thirty-day period.

The clinical picture presented by nearly all patients on admission to the hospital was that of an acute and moderately severe febrile illness. The symptoms were such as are frequently associated with many other acute infectious diseases and were in no way pathognomonic. Chief among them was fatigue, which was experienced to a moderate or marked degree by all patients in the series. Aches and pains in the muscles or joints, or both, occurred in 15 patients, the pains, which were usually dull, intermittent, multiple and not clearly localized, often recurred far into the period of convalescence.

Headache was present during the acute phase of chills. Other symptoms included mild nonproductive cough, moderate nausea, occasional vomiting.

TABLE 1 Summary of Clinical and Laboratory Data in 9 Patients with Acute Brucellosis

CASE No	AGE	SEX	AGGLUTININ TITER		OPSONOCYTOPHAGIC INDEX			BRUCELLERGEN SKIN TEST				
			BEFORE IMMUNIZATION	AFTER IMMUNIZATION	AFTER INFECTION	BEFORE IMMUNIZATION	HIGHEST READING AFTER IMMUNIZATION	LOWEST SUBSEQUENT READING BEFORE ONSET OF ILLNESS	HIGHEST READING AFTER INFECTION	BEFORE IMMUNIZATION	AFTER IMMUNIZATION BUT BEFORE ILLNESS	ACTIVATION AFTER INFECTION
1	26 yr	F	Negative	1:200	1:6400	Negative	Marked	Slight	Moderate	Negative	—	Yes
2	24	M	Negative	Negative	1:6400	Negative	Negative	Negative	Slight	Negative	Negative	No
3	21	F	Negative	—	1:3200	Negative	Negative	Negative	Moderate	Negative	—	No
4	28	M	—	—	1:3200	Moderate	Marked	Moderate	Marked	Negative	Positive	No
5	26	F	—	1:400	1:3200	—	Marked	Moderate	Moderate	Negative	Negative	Yes
6	24	F	Negative	1:200	1:6400	Negative	Marked	Negative	Moderate	Negative	Negative	Yes
7	25	M	Negative	—	1:1600	Negative	Moderate	Moderate	Moderate	Negative	Negative	No
8	28	M	1:25	1:100	1:1600	Negative	Moderate	Moderate	Moderate	Negative	Negative	Yes
9	21	F	—	—	1:1600	Negative	Marked	Moderate	Moderate	Negative	Negative	Yes

prominent symptom in a few. Approximately half the patients experienced one or several shaking and photophobia. Diarrhea was present in 4 patients, being moderately severe in two.

Signs

Physical examination in most cases disclosed no abnormalities other than fever and prostration. The fevers were characterized by great variability. The fevers were usually irregular and intermittent in type,

TABLE 1 (Continued)

Case No.	Chief Symptoms	Dates of Acute Illness	Blood Cultures		Chemotherapy	Blood Levels per 100 cc	Temperature over 99°F		Present Status of Patient
			Strain	Dates Isolated	Dates Negative		Before Treatment days	After Treatment days	
1	Moderate fatigue slight cough myalgia and moderate headache	Jan 5-28 Apr 3-10	<i>Br suis</i>	Jan 12 Jan 16 Jan 24 Apr 5 Apr 6 Apr 7		3,500,000 units of penicillin and 64 gm of sulfadiazine (Jan 24-Feb 7) None	7-11 mg	13 4	Asymptomatic
2	Moderate fatigue slight cough, severe headache generalized arthralgia and myalgia and slight diarrhea	Feb 3-28	<i>Br suis</i>	Feb 19	Feb 17 Feb 20	2,100,000 units of penicillin and 54 gm of sulfadiazine (Feb 24-Mar 5)	9-10 mg	7 3	Asymptomatic
3	Marked fatigue mild photophobia slight cough shaking chills generalized arthralgia and myalgia moderate nausea and vomiting and severe diarrhea	Mar 1-Apr 26 May 7-27 June 10-Nov 7	<i>Br suis</i>	Mar 31 Apr 3 Apr 17 May 11 May 15 May 16 May 18 May 19 Oct. 19 Oct. 25 Nov 6	Mar 7 Mar 13 Apr 16 Apr 17 Apr 18 Apr 21 May 11 May 15 May 16 May 18 May 19 Oct. 19 Oct. 25 Nov 6	810,000 units of streptomycin (Apr 18-20) 15,800,000 units of streptomycin (May 19-26) None	1-3 units	18 12 9	Persistent fatigue
4	Moderate fatigue and generalized myalgia	July 15-28	<i>Br suis</i>	July 16 July 17 July 18	July 19 July 20 July 28	23,000,000 units of streptomycin (July 22-27) None	16-47 units	7 6	Unknown
5	Moderate fatigue, slight cough shaking chills moderate headache generalized arthralgia and myalgia and slight nausea	Aug 6-10 Aug 17-Sept. 3 Sept. 13-27 Nov 9-12 Nov 25-28	<i>Br melitensis</i>	Aug 18 Sept. 22	Aug 7 Aug 8 Aug 25 Aug 27 Aug 28 Aug 29 Aug 30 Sept. 18 Sept. 19 Sept. 20 Sept. 23 Sept. 24 Nov 10 Nov 14 Nov 25 Nov 26	20,500,000 units of streptomycin (Aug 25-30) 169 gm of sulfadiazine (Sept 24-Oct 25) None None	3-28 units	2 10 2	Asymptomatic
6	Marked fatigue slight cough shaking chills severe headache generalized arthralgia and myalgia and moderate nausea and vomiting	Sept 3-23 Oct. 7-29	<i>Br melitensis</i>	Sept 8 Sept. 9 Sept. 10 Sept. 12 Oct. 12 Oct. 13	Sept. 10 Sept. 11 Sept. 12 Oct. 5 Oct. 8 Oct. 9 Oct. 11 Oct. 12 Oct. 13 Oct. 15 Oct. 23	136 gm of sulfadiazine (Sept 10-Oct 1) 28 gm of sulfadiazine (Oct 15-17)	6-14 mg	7 8 17	Asymptomatic
7	Marked fatigue severe headache, generalized arthralgia and myalgia moderate nausea and vomiting and slight diarrhea	Sept. 29-Oct. 15 Nov 9-16 Nov 24-Dec. 14	<i>Br melitensis</i>	Sept. 22 Nov 10 Nov 30	Sept. 20 Sept. 21 Sept. 23 Sept. 24 Nov 12 Nov 13 Nov 16 Nov 24 Nov 27 Dec. 1	177 gm of sulfadiazine (Sept 24-Oct. 24) None None	8-12 mg	4 3 3	Persistent fatigue
8	Moderate fatigue slight headache and generalized myalgia	Sept 19-Oct. 18	<i>Br suis</i>	Sept. 22 Sept. 24 Sept. 25 Sept. 28	Sept. 29 Oct. 8 Oct. 13 Oct. 24 Oct. 31	180 gm of sulfadiazine (Sept. 27-Oct. 26)	7-10 mg	8 5	Asymptomatic
9	Slight fatigue slight cough and moderate headache	Sept 10-25 Oct. 8-29			Sept. 11 Sept. 12 Oct. 4 Oct. 22	164 gm. of sulfadiazine (Sept. 24-Oct. 24) None	10-14 mg	3 1	Asymptomatic

abnormalities other than fever and prostration. The temperature charts exhibited by these patients with temperatures highest in the late afternoon, and showing diurnal swings of 1 to 4°. Most patients

had peak temperatures of 102 to 104°F during the acute illness. Four patients showed definite periodic undulations of fever, with intervening periods of apyrexia. One patient (Case 11) experienced a four-day episode of sustained high temperature and great prostration, reminiscent of the malignant type of brucellosis. The total number of days of fever — that is, a temperature above 99°F orally — varied from thirteen to ninety-seven, and averaged thirty-

with diarrhea. In a few cases, joint pains were accompanied by joint tenderness, but there were no other objective signs of arthritis. Herpes febrilis appeared in 2 cases.

Clinical Course

The course of patients infected with *Brucella suis* was not discernibly different from that of patients

TABLE 2 Summary of Clinical and Laboratory Data in 8 Patients with Acute Brucellosis

Case No.	Age	Sex	Agglutinin Titer	Highest Agglutinin Titer		Opsonocytophagic Index				Brucellergen Skin Test		
			Before Immunization	After Immunization	After Infection	Before Immunization	Highest Reading After Immunization	Lowest Subsequent Reading Before Onset of Illness	Highest Reading After Infection	Before Immunization	After Immunization But Before Illness	Activation After Infection
10	26 yr	M	Negative	1:400	1:3200	Negative	Marked	Marked	Moderate	Negative	Negative	Negative
11	27	M	—	1:200	1:3200	—	Marked	Moderate	Moderate	Negative	Negative	No
12	26	M	Negative	1:50	1:3200	Negative	Moderate	Negative	Moderate	Negative	Negative	No
13	26	M	1:25	1:100	1:3200	Slight	Moderate	Moderate	Moderate	Negative	Negative	No
14	21	M	—	—	1:3200	Negative	Negative	Negative	Moderate	Negative	Negative	Yes
15	25	M	Negative	1:25	1:12800	Marked	Moderate	Negative	Marked	Negative	Negative	Yes
16	22	F	—	—	1:1600	Negative	Marked	Marked	Moderate	Negative	Negative	No
17	22	F	—	—	1:2560	Negative	Marked	Moderate	Marked	Negative	Negative	Yes

five days. In general, the intensity of symptoms and the degree of prostration were directly proportional to the degree of fever. These descriptions are based on observations made when the patients were not receiving antipyretic drugs.

The spleen could be palpated in only 1 patient (Case 3), and then only after she had suffered pulmonary infarcts. Two patients exhibited moderate generalized abdominal tenderness coincidental

infected with *Br. melitensis*. Only one episode of acute illness occurred in 5 patients, two episodes in 9 and three episodes in 2, whereas 1 patient experienced five distinct attacks. In some cases the initial attack was the severest, and in others, subsequent attacks were more prostrating and prolonged. In patients who had an undulating type of fever, the peak of temperature and the intensity of symptoms tended to diminish with succeeding undulations.

Increased physical activity was often followed by relapses. Patients were therefore kept in bed during febrile periods and were permitted only gradual increases in activity during convalescence. The convalescent period was long because of a persistent state of lassitude and easy fatigability that lasted for months after all other evidence of illness had disappeared. The shortest illness was observed in Case 2, in which the patient had recovered, appar-

LABORATORY DATA

Blood Cultures

In taking blood cultures, two types of medium were used routinely. On each occasion, 15 cc of blood was withdrawn, of which half was added to 100 cc of nutrient broth and half to 100 cc of Bacto-Tryptose broth. All blood cultures were incubated under aerobic conditions at 37°C, and were

TABLE 2 (Continued)

Case No	Chief Symptoms	Dates of Acute Illness	Blood Cultures		Chemotherapy	Blood Levels	Temperature over 99°F		Present Status of Patient	
			Strain	Dates Isolated			Dates Negative	Before Treatment		After Treatment
10	Moderate fatigue, generalized arthralgia and myalgia	Sept. 5-13	<i>Br melitensis</i>	Sept. 11	Sept. 11	1.9 gm of sulfadiazine (Sept. 18-Oct. 11)	6-12 mg	0	0	Asymptomatic
11	Marked fatigue, moderate cough, shaking chills, severe headache, generalized arthralgia and myalgia, moderate nausea and vomiting and severe diarrhea	Oct. 28-Nov. 3 Aug. 13-Sept. 15	<i>Br melitensis</i>	Aug. 26 Aug. 27 Aug. 30 Aug. 31 Oct. 12 Oct. 13 Oct. 15 Nov. 8	Oct. 19 Oct. 5 Oct. 25 Nov. 5 Nov. 15	151 gm of sulfadiazine (Aug. 30-Sept. 24)	0-15 mg	10	9	Persistent fatigue
12	Moderate fatigue, shaking chills, slight headache and generalized arthralgia and myalgia	Sept. 9-26 Nov. 5-Dec. 5	<i>Br suis</i>	Sept. 14 Sept. 16 Nov. 6 Nov. 8 Nov. 16 Nov. 21 Nov. 26 Dec. 8	Sept. 12 Sept. 15 Nov. 9 Nov. 12 Nov. 23 Nov. 25 Dec. 8	137 gm of sulfadiazine (Sept. 19-Oct. 11)	5-10 mg	7	4	Asymptomatic
13	Marked fatigue, shaking chills, moderate headache, generalized arthralgia and myalgia and moderate nausea	Aug. 27-Sept. 3 Sept. 28-Dec. 12	<i>Br suis</i>	Aug. 31 Sept. 1 Oct. 4 Oct. 5 Oct. 21 Oct. 22 Oct. 23 Oct. 29 Nov. 4 Nov. 7 Nov. 21 Dec. 3	Nov. 26 Dec. 6	132 gm of sulfadiazine (Sept. 1-21)	9-14 mg	1	5	Asymptomatic
14	Marked fatigue, shaking chills, moderate headache and generalized arthralgia and myalgia	Sept. 22-Oct. 2 Nov. 20-Dec. 7	<i>Br suis</i>	Sept. 28 Sept. 29 Oct. 4 Dec. 1	Sept. 30 Oct. 9 Dec. 2 Dec. 8 Dec. 20	175 gm of sulfadiazine (Sept. 29-Oct. 28)	6-14 mg	2	5	Asymptomatic
15	Marked fatigue, severe headache, generalized arthralgia and myalgia and moderate nausea and vomiting	Oct. 10-29 Nov. 28-Jan. 3	<i>Br melitensis</i>	Oct. 17 Oct. 18 Oct. 20 Oct. 21 Dec. 1 Dec. 7	Oct. 30 Nov. 30 Dec. 2 Dec. 16 Dec. 18 Dec. 31	172 gm of sulfadiazine (Oct. 18-Nov. 16)	7-15 mg	7	11	Persistent fatigue
16	Moderate fatigue, shaking chills and moderate headache	July 22-Aug. 17	<i>Br melitensis</i>	July 27 July 28 July 29 July 30	July 24 July 31 Aug. 10	None				Persistent fatigue
17	Moderate fatigue and generalized arthralgia and myalgia	Oct. 20-Nov. 26			Oct. 25 Nov. 2	None				Asymptomatic

ently completely, four months after the onset. The longest illness was observed in Case 3, and after twelve months the patient continues to have occasional symptoms. Five of the other patients still complain of easy fatigability five to twelve months after the onset of disease. None of the patients exhibited signs of localized *Brucella* infection in any particular organ or system.

subcultured repeatedly on tryptose-agar plates. All cultures were held for fourteen days before being discarded. In the majority of cases the organisms grew equally well in both mediums. When specimens were taken during sulfadiazine therapy, 5 mg of para-aminobenzoic acid was added to each 100 cc of medium. When cultures were taken during streptomycin therapy 25 mg of cysteine hydro-

chloride was added to each 100 cc of medium to inhibit the action of this antibiotic

Br suis was isolated from the blood in 8 cases, and *Br melitensis* in 7. One or more positive blood cultures were obtained in most patients during the initial acute phase of illness, and usually again during subsequent febrile relapses. It is worth emphasizing the fact that blood cultures were occasionally positive during periods when symptoms were minimal and when temperatures were normal throughout the day.

Agglutination Tests

The macroscopic tube-agglutination technic used in the United States Army² was employed. The antigen was a standardized suspension of *Br abortus* prepared at the Army Veterinary School. Titers were expressed in terms of the highest final dilution of serum at which agglutination was visible with the aid of a concave magnifying mirror (Table 1). Prior to immunization no titer exceeded 1:25, and after immunization none exceeded 1:400. This serologic response to immunization usually fell after one or two months.

In all patients there was a sharp rise in agglutinins within three or four weeks of the onset of illness. Maximum titers of 1:1600 to 1:12,800 were reached in one or two months, after which the titers usually dropped slowly. After six months the agglutinin titers varied from 1:400 to 1:1600.

The height of the agglutinin titer was not proportional to the severity of illness, nor did it show consistent variations with remissions or exacerbations. It can be said that agglutinin determinations were useful for diagnosis but not for prognosis.

Opsonocytaphagic Index

This test* was performed essentially as outlined by Huddleson.³ The opsonocytaphagic index was usually altered by immunization so that the interpretation of subsequent determinations was difficult. Table 1 shows that the indexes increased in 9 patients after infection as compared with preinfection determinations, whereas in 8 patients they remained at the same level or actually fell. In this series the opsonocytaphagic index was therefore of questionable diagnostic value. As with the agglutination test, the index showed no predictable variation with alterations in clinical course and thus did not aid in prognosis.

Skin Tests

None of the 17 patients showed skin sensitivity to 0.1 cc of undiluted brucellergen administered intradermally prior to immunization. The test was repeated after immunization and in one patient was

positive. Skin tests were not performed after the onset of illness because of the danger of precipitating systemic reactions during the course of active infection. A phenomenon of great interest was observed in 8 patients after the onset of clinical illness: erythema and edema appeared spontaneously at the sites of the previous skin tests and vaccine injections, and in 1 case the inflammatory lesion progressed to actual necrosis. It must be emphasized that these delayed inflammatory phenomena developed in 6 patients from four to six months, and in 2 patients one and sixteen months, respectively, after the administration of the brucellergen or vaccine. The lesions appeared during the acute illness, faded during remissions, and reappeared with subsequent exacerbations.

Chest X-Ray Examination

Roentgenograms were taken routinely on admission and at intervals thereafter. They were consistently normal, except in Case 3, in which the patient, while receiving continuous intravenous streptomycin therapy, developed thrombophlebitis followed by bilateral pulmonary infarcts.

White-Cell Counts

The blood in all cases showed a leukopenia with a relative lymphocytosis. This finding frequently persisted beyond the stage of acute illness. There were no abnormal cell forms.

TREATMENT

A summary of the treatment in these cases is presented in Table 1. Eleven patients received sulfadiazine, 2 were given penicillin and sulfadiazine simultaneously, 3 received streptomycin, and 2 were given only symptomatic therapy. One patient (Case 5), who was given a course of sulfadiazine during a relapse following streptomycin therapy, is included in both groups. The table shows the duration of fever before and after initiation of chemotherapy for each patient. These figures cover the span of a single acute episode and afford a rough index of the clinical response to the given chemotherapeutic agent.

Sulfadiazine Therapy

Unpublished experimental data from the technical laboratory at this station indicated that thirty days of sulfadiazine therapy in guinea pigs infected with *Br suis* resulted in a definite modification of the disease. Because of these encouraging results, 11 patients were treated with sulfadiazine for periods of twenty to thirty days. Blood levels of free sulfadiazine were maintained well in excess of concentrations required to inhibit the growth of *Br suis* in vitro. There was no clear-cut, abrupt amelioration of symptoms, the temperatures dropped to normal in one to eleven days after the beginning of treatment. In all but 1 of these 11 patients, after the

*The cells were categorized according to the degree of phagocytosis, as "negative," "slight," "moderate" or "marked" according to Huddleson's criteria. The category containing the greatest number of cells was then taken as the final reading for the slide. When two categories contained an equal number of cells, the two remaining categories were considered in determining the final reading.

temperature had returned to normal, there were no marked elevations during the remainder of the therapeutic period. Ten patients had positive blood cultures prior to treatment. Blood cultures were taken during treatment in 6 cases and were positive in 4, on the second to sixth days of treatment. The evaluation of therapeutic efficacy of a drug is admittedly difficult in a disease whose course is as variable as that of brucellosis. Nevertheless, there seemed little clinical evidence that sulfadiazine therapy had benefited these patients. There was in fact ample evidence that none of them had been cured, for all 11 patients in this group suffered one or more relapses after cessation of therapy. During these relapses, blood cultures were positive in 7 cases, negative in 3 and were not taken in one.

Strains of *Brucella* isolated before, during and after therapy were tested in vitro for sensitivity to sulfadiazine. There was no demonstrable decrease in sensitivity as a result of therapy.

Simultaneous Administration of Sulfadiazine and Penicillin

The 2 patients in this group received treatment for twelve and nine days respectively. Penicillin was given intramuscularly, and sulfadiazine by mouth. In neither case was there a definite clinical response to therapy. One patient (Case 1) had a short relapse with positive blood cultures subsequent to treatment, since that time she has been well. The other (Case 2) has apparently recovered completely.

Streptomycin Therapy

Streptomycin hydrochloride* was submitted to clinical trial in 3 cases. Studies of absorption and excretion of streptomycin in these patients are reported elsewhere.⁴ The drug was administered intramuscularly or intravenously. There was no apparent clinical response in these patients. All 3 had positive blood cultures prior to treatment, and 2 (Cases 3 and 5) had negative cultures during treatment. No blood cultures were taken during treatment in the third case. In Cases 3 and 5 the

patients had one or more relapses, one with positive blood cultures and the other without. The subsequent course in Case 4 has not been ascertained, since we were unable to observe the patient following recovery from the initial episode.

Symptomatic Therapy

As stated above, the symptoms in most patients were directly proportional to the degree of fever. It was found that acetylsalicylic acid in doses of 0.3 to 0.6 gm administered regularly every four hours resulted in a sharp drop in fever and a coincidental decrease in malaise, muscular aching and headache.

SUMMARY AND CONCLUSIONS

Clinical and laboratory data from 17 cases of brucellosis are presented. The patients were laboratory workers engaged in investigative work with strains of *Brucella suis* and *Br. melitensis*.

Eleven patients were treated with sulfadiazine for periods of twenty to thirty days. There was no evidence that this therapy altered the natural course of the disease. Of the remaining patients, 3 were treated with streptomycin, and 2 with penicillin and sulfadiazine simultaneously. From this limited clinical experience there was no indication that these drugs were of therapeutic benefit.

Addendum. The status of 14 out of these 17 patients was ascertained as of January 1, 1947, approximately two years after the occurrence of the first case. The status of 3 patients (Cases 2, 10 and 17) is unknown. One patient (Case 3) has had more than ten febrile episodes since the onset of her illness, and continues to experience severe symptoms. Three patients (Cases 4, 13 and 16), who are back at normal activity and no longer exhibit fever, report mild occasional symptoms. The remaining 10 patients are well, following illnesses lasting from one to twelve months (average, slightly less than six months).

REFERENCES

- 1 Meyer, K. F., and Eddie, B. Laboratory infections due to *Brucella*. *J. Infect. Dis.* 68:24-32, 1941.
- 2 *Laboratory Methods of the United States Army*. Edited by J. S. Simmons and C. J. Gentzow. Fifth edition. 823 pp. Philadelphia: Lea & Febiger, 1944.
- 3 Huddleson, I. F., Hardy, A. V., Debono, J. E., and Giltner, W. *Brucellosis in Man and Animals*. Second edition. 379 pp. New York: Commonwealth Fund, 1943.
- 4 Kornegay, G. B., Forgacs, J., and Henley, T. F. Studies on streptomycin. II. Blood levels and urinary excretion in man and animals. *J. Lab. & Clin. Med.* 31:523-534, 1946.

*Kindly supplied by Merck and Company, Rahway, New Jersey.

MEDICAL PROGRESS

STREPTOMYCIN (Concluded)*

II Clinical Uses

TOM F. PAINE, M.D.,† Roderick Murray, M.D.,‡ AND Maxwell Finland, M.D.§

BOSTON

THE present knowledge of the clinical usefulness of streptomycin is largely the result of a co-ordinated effort by the streptomycin producers with the medical departments of several governmental agencies, including the Army, Navy, Public Health Service and Veterans Administration, as well as many physicians throughout the country. Under the guidance of the Committee on Chemotherapeutics and Other Agents of the National Research Council and with funds contributed by several pharmaceutical and chemical companies, limited amounts of streptomycin were apportioned to civilian physicians for the purpose of investigating its effectiveness in a wide variety of conditions. Much valuable information was thus accumulated in a short time, although there is still need for further investigation.²⁰² The practical aspects of streptomycin administration, the results of treatment of various infections and the toxic effects observed are considered below.

ADMINISTRATION AND DOSAGE

Streptomycin, as either the hydrochloride or the sulfate, is usually supplied as a dry, sterile powder in airtight rubber-capped vials each containing the equivalent of 1.0 gm (1,000,000 units) of the streptomycin base. Streptomycin and its salts are reasonably stable, but storage at a temperature not above 15°C is recommended. Solutions are less stable than the dry powder and should be kept in a refrigerator.⁴⁰

Streptomycin may be administered parenterally, orally or locally. The intramuscular route is the one generally used for parenteral administration. The subcutaneous route may be used, but it is likelier to cause pain and local irritation. Intravenous injections are used chiefly to attain high concentrations rapidly or to avoid local irritation, immediate systemic reactions, however, are more frequent with this route.²⁰² Various investigators have given the drug orally.^{45, 183, 202, 203} Topically,

streptomycin has been applied intrathecally,^{72, 80, 81-119, 202, 204, 205} intracisternally,²⁰⁶ into the lateral cerebral ventricles, through the anterior fontanelle, in infants,⁸¹ intrapleurally,^{206, 207} intraperitoneally,²⁰² cystoscopically into the urinary bladder and kidney pelvis,³¹ by inhalation,^{82, 202, 208} intratracheally,²⁰⁹ by gauze soaks to cutaneous areas⁷⁴ and by drops on the conjunctiva,^{210, 211} into the nose²¹² and into the external auditory canal.⁸²

Parenteral Administration

The object of parenteral streptomycin is to maintain an inhibitory concentration in the blood stream and at the sites of infection. The concentration of streptomycin required to inhibit different bacteria varies considerably, and clinical results do not always correspond to the in vitro sensitivity of the bacteria.^{57, 62, 84, 146, 203} On general principles, it seems wise to administer large doses of streptomycin and thus to maintain high blood and local concentrations.^{202, 213-216} In adults the intramuscular administration of 1.0 gm of streptomycin at six-hour intervals is ordinarily adequate for most infections. This dose is usually well tolerated and provides a good margin of therapeutic safety, but smaller doses have generally been used.²⁰² Somewhat larger doses—up to 8 gm a day—may be given to adults if indicated.[¶] Infants and children require smaller doses, 30 to 75 mg per pound of body weight, or a total of 0.25 to 2.0 gm daily should be adequate.^{80, 81, 204}

Intermittent intramuscular injection is the parenteral method of choice. The gluteal regions, the lateral aspects of the thighs and sometimes the triceps muscle may be used in rotation. Each gram of streptomycin is dissolved in 4 or 5 cc of sterile, pyrogen-free distilled water or physiologic saline solution. This volume can be administered with only slight discomfort to the patient, but, if desired, 1 cc of 1 per cent procaine hydrochloride may be added to each 4 cc of streptomycin solution. A more dilute solution—0.1 gm per cubic centimeter—may be used for intramuscular injections of 0.5 gm or less. The solution should be clear and free of undissolved particles.²⁰² For continuous intra-

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¶It has been stated that infections will not be influenced regardless of the amount of streptomycin given, if the infecting organism grows in 16 microgm per cubic centimeter and furthermore that no additional benefit may be expected regardless of the type or severity of the infection from doses greater than 3.0 gm a day.⁴¹ This is at variance with our experience.

venous administration 1 or 2 gm may be dissolved in a liter of physiologic saline solution and given at the rate of about twenty-five drops a minute. For single or intermittent intravenous injections, 1.0 gm of streptomycin is dissolved in 20 cc or more of physiologic saline solution and injected slowly.⁶⁵

Oral Administration

Streptomycin is absorbed only to a slight extent after its ingestion, and little appears in the bowel contents during parenteral administration. The ingestion of 2 to 5 gm daily in orange juice or other liquids is well tolerated and produces a marked reduction in the number of most of the susceptible organisms in the feces.^{64, 202} The method has been used in preparing patients for operations on the bowel.^{65, 217}

Local Administration

Intrathecal injection. Since adequate diffusion of streptomycin from the blood into the cerebrospinal fluid cannot be relied on,^{69-73, 218, 219} systemic therapy should be supplemented by local administration in the treatment of meningitis. Doses of 50 to 200 mg dissolved in 5 to 10 cc of physiologic saline solution may be given intrathecally every twelve to forty-eight hours.^{202, 204, 205} Injections of more than 50 mg, however, may produce signs of meningeal irritation.^{71, 119, 206} As much as 25 mg a day has been given intraspinally, intraventricularly or directly into a meningocele sac in infants who were about two weeks old.⁶¹ Streptomycin has been injected safely into infected lateral cerebral ventricles⁶¹ and into the basal cistern.²²⁰

Inhalation. Streptomycin may be administered for bronchopulmonary disease either as an aerosol²⁰³ or by intratracheal instillation.²⁰⁹ Doses of 50 to 100 mg in 1 cc of physiologic saline solution may be nebulized at intervals of two to six hours.²⁰² More concentrated solutions are unsatisfactory for aerosols and are wasteful because their viscosity causes frothing and because the nebulizer tends to clog.

Other routes. Streptomycin has been applied directly to the urinary bladder and kidney pelvis through a cystoscope or an indwelling catheter,²¹ but such an approach offers no advantage over parenteral therapy since the drug is usually excreted in a high concentration in the urine. The antibiotic has been injected intrapleurally in the treatment of empyema.^{202, 205} The optimum dosage by this route is not known, but 50 to 500 mg in 25 to 100 cc of physiologic saline solution can probably be introduced safely into the infected pleural cavity. As much as 1 gm has been put into the pentoneal cavity at the time of operation.⁷⁴ Solutions containing 10 mg per cubic centimeter have been applied to the conjunctiva (two drops every four hours) without harmful effects.^{210, 211} Streptomycin in concentrations up to 25 mg per

cubic centimeter has been instilled into the auditory canals of patients with suppurative otitis without ill effects.²²¹ It has been used as nose drops in a concentration of 10 mg per cubic centimeter, five drops being administered into each nostril every three hours.²¹² It has been applied locally to wounds in concentrations of 0.2 to 0.5 mg (200-500 units) per cubic centimeter.⁷⁴

URINARY-TRACT INFECTIONS

Streptomycin has been used extensively in the treatment of urinary-tract infections.^{21, 50, 74, 84-86, 194, 202, 203, 212-214, 222-225} The report of the National Research Council²⁰² includes 409 cases with an overall recovery rate of 42 per cent based mostly on short periods of observation. Similar results were obtained in 264 cases treated in Army hospitals.²²⁵ Almost all civilian patients had previously been treated ineffectively with sulfonamides and penicillin. A considerable number improved during streptomycin treatment but then relapsed, generally during the first week after cessation of therapy.

Several points have been emphasized. Many patients show definite clinical improvement without bacteriologic remission. Many who improve are cured bacteriologically but do not recover clinically because the underlying anatomic irregularities are not corrected. Infections due to a single organism respond oftener than mixed infections do. Rapid development of resistance during treatment is frequent and accounts for many of the failures. A minimal follow-up period of a week is essential before any patient with a urinary-tract infection can be considered recovered. All cases should be carefully studied to determine the nature of the infection, the sensitivity of the organisms, the reaction of the urine and the presence of underlying anatomic lesions.^{202, 213}

In the treatment of urinary-tract infections in patients with neurogenic bladders following spinal injuries streptomycin has proved useful only for controlling the severe infections and associated septicemias.^{21, 194, 225} In such cases only 28 per cent of patients improved, as compared with 54 per cent among those without spinal-cord injuries.²²⁵ Streptomycin-resistant strains often developed in these cases, and even when this did not happen, cessation of therapy was promptly followed by the appearance of new infections. There was no advantage in the use of streptomycin locally.²¹

Alkalinization of the urine may be an important adjunct to streptomycin therapy of urinary-tract infections because of the increased activity of streptomycin in an alkaline medium.⁶⁰ In 21 cases studied at the Boston City Hospital the first 7 patients were treated without alkalis, and failures in 6 cases were associated with the development of highly resistant strains of bacteria during treatment.⁸⁵ On similar doses of streptomycin, usually 4 to 6 gm daily, but with alkalinization of the urine

MEDICAL PROGRESS

STREPTOMYCIN (Concluded)*

II Clinical Uses

TOM F. PAINE, M.D.,† RODERICK MURRAY, M.D.,‡ AND MAXWELL FINLAND, M.D.§

BOSTON

THE present knowledge of the clinical usefulness of streptomycin is largely the result of a coordinated effort by the streptomycin producers with the medical departments of several governmental agencies, including the Army, Navy, Public Health Service and Veterans Administration, as well as many physicians throughout the country. Under the guidance of the Committee on Chemotherapeutics and Other Agents of the National Research Council and with funds contributed by several pharmaceutical and chemical companies, limited amounts of streptomycin were apportioned to civilian physicians for the purpose of investigating its effectiveness in a wide variety of conditions. Much valuable information was thus accumulated in a short time, although there is still need for further investigation.²⁰² The practical aspects of streptomycin administration, the results of treatment of various infections and the toxic effects observed are considered below.

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Intermittent intramuscular injection is the parenteral method of choice. The gluteal regions, the lateral aspects of the thighs and sometimes the triceps muscle may be used in rotation. Each gram of streptomycin is dissolved in 4 or 5 cc of sterile, pyrogen-free distilled water or physiologic saline solution. This volume can be administered with only slight discomfort to the patient, but, if desired, 1 cc of 1 per cent procaine hydrochloride may be added to each 4 cc of streptomycin solution. A more dilute solution — 0.1 gm per cubic centimeter — may be used for intramuscular injections of 0.5 gm or less. The solution should be clear and free of undissolved particles.²⁰² For continuous intra-

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¶It has been stated that infections will not be influenced regardless of the amount of streptomycin given if the infecting organism grows in 16 microgm per cubic centimeter and furthermore that no additional benefit may be expected, regardless of the type or severity of the infection from doses greater than 30 gm a day.¹¹ This is at variance with our experience.

amide or penicillin treatment. Infections due to *H influenzae* may be frequent and serious in infants and children. Several streptomycin-treated cases due to these organisms have been reported^{74-76, 202-209, 215, 236-238}. A few cases of acute pneumonitis, apparently due to *H influenzae*, responded favorably to streptomycin after failing to improve on sulfonamides and penicillin^{82, 200, 215}. The institution of streptomycin therapy in these patients was followed by prompt clinical improvement and disappearance of *H influenzae* from the sputum.

Pneumonia due to Friedländer bacillus has a high mortality rate²⁹ that has not been strikingly influenced by sulfonamides or penicillin. The response to streptomycin in such cases has not been uniformly favorable,^{74, 82, 202-225, 240} in spite of the fact that the causative organism, *K pneumoniae*, is usually quite sensitive to the drug. The results are readily understandable when one considers the pathology of this disease, which is marked by the early development of multiple pulmonary cavities filled with viscid exudate. Four cases of pneumonia due to Friedländer bacillus have been reported in which streptomycin therapy begun after several days of ineffective sulfonamide or penicillin therapy, or both, resulted in prompt improvement^{202-215, 241}. One case is reported in which a resistant strain of *K pneumoniae* developed in the sputum after two days of streptomycin therapy, the patient nevertheless improved promptly and eventually recovered⁸². In view of the high mortality in pneumonia due to Friedländer bacillus, the prompt institution of large doses of streptomycin — preferably 10 gm every four hours in adults — seems indicated.

In a case of severe pharyngitis apparently due to *P aeruginosa* in a child with leukemia, the organisms quickly disappeared from the throat following institution of streptomycin therapy²⁰².

Chronic Infections

Chronic bronchiectasis is a distressing and debilitating disease. Treatment of such cases with penicillin aerosol in conjunction with postural drainage has proved to be of much help in reducing the amount of sputum, decreasing the incidence and severity of the episodes of superimposed pneumonitis and in preparing the patients for operations²⁴¹. Penicillin, however, eliminates only the penicillin-sensitive organisms, and in some patients the infection persists, owing to the presence of the penicillin-insensitive organisms, mostly gram-negative bacilli. The response of such cases to streptomycin has been encouraging^{82, 208, 209, 218}. The volume of sputum diminishes, and gram-negative bacilli disappear promptly following inhalations of streptomycin aerosol²⁰⁸. The total daily dose of nebulized streptomycin used in some of these cases was 0.5 gm. in 20 cc of saline solution daily²⁰⁸. Similar cases have been treated by daily intratracheal instillations of 5 cc of streptomycin solution contain-

ing 10 mg per cubic centimeter, with similar favorable results²⁰⁹.

The ease of administration of antibiotics by aerosol offers a simple but often effective means of treating patients with chronic bronchiectasis and chronic bronchitis. Whether or not concomitant parenteral therapy in these patients is advantageous has not been determined, and the problem of development of resistance by the organisms under aerosol treatment must be investigated further⁸². The rational aerosol treatment of chronic bronchiectasis may well involve the combined use of penicillin and streptomycin²⁰⁸. Such treatment is probably only palliative but may offer considerable relief from the distressing symptoms, lessen the frequency of complications and possibly arrest the progress of the disease.

Empyema

Several cases of empyema thoracis have been treated with variable results. Details in these cases are lacking^{202, 225}.

Nasal and Sinus Infections

A case of chronic sinusitis due to *K pneumoniae*²¹⁷ was treated with 100 mg of streptomycin aerosol five times daily given by the method of Barach and his associates²⁴². The patient had undergone two episodes of pneumonia due to Friedländer bacillus during the previous two years. The Friedländer bacilli were promptly eliminated from the nose and sputum. Four patients with ozena possibly due to *K pneumoniae* were treated by parenteral streptomycin, with symptomatic improvement²⁴³.

BACTERIAL ENDOCARDITIS

There are few reports on the use of streptomycin in bacterial endocarditis. Although endocarditis due to gram-negative bacilli is infrequent, the early use of streptomycin in such cases seems indicated. The only reported recovery occurred in a case of subacute bacterial endocarditis due to an unidentified gram-negative bacillus²⁴⁴. Streptomycin therapy was started in that case after several days of treatment with penicillin and sulfadiazine. Although cultures had already become negative, it was thought that the streptomycin helped effect the cure.

The usefulness of streptomycin in endocarditis, however, may not be limited to infections with gram-negative bacilli. Indeed, the drug may be superior to penicillin in certain infections, such as those due to enterococci and nonhemolytic or alpha-hemolytic streptococci, that are resistant to the concentrations of penicillin maintained in the blood but sensitive to those attainable with streptomycin. Three cases of subacute bacterial endocarditis caused by such organisms were reported¹³². Two of them were due to nonhemolytic streptococci that were inhibited by 1 unit of streptomycin but required 6 units of penicillin in one case and 4 units in the other. Treatment with streptomycin was

during the streptomycin treatment in the remaining 14 cases, 8 patients were cured and 6 were temporarily improved. Only 1 of the latter developed a resistant organism during treatment, and the other 5 had recurrences of infection following the cessation of streptomycin, possibly because of uncorrected anatomic defects in the urinary tract. These patients were followed for two to four months. Alkalinization of the urine was usually accomplished by the oral administration of 1 gm each of sodium bicarbonate and potassium citrate every four hours, but larger doses were sometimes required. The urine was checked frequently during therapy to ensure that an alkalinity actually existed.

Albright²²⁹ has had good results with streptomycin in cases of urinary infections associated with renal stones. Alkalinization with sodium citrate was used routinely in his cases. Kane and Foley²³⁰ treated 40 cases due to gram-negative bacilli at the Massachusetts General Hospital and followed them for four to eight months. Cures were obtained in 30 cases, 4 patients were improved, and 6 cases were failures. Alkalies were given to all, and a resistant strain developed in only 1 case.

INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

Streptomycin has proved of great value in the treatment of infections of the central nervous system due to gram-negative bacilli. It has been used most extensively in meningitis caused by *Haemophilus influenzae*.

Meningitis due to H. Influenzae

The report of the National Research Council²⁰² includes 100 cases. 66 of the patients were cured clinically and bacteriologically while under treatment, 13 improved under treatment and finally recovered, 1 improved but relapsed, 3 showed no effect, and 17 died. Eighteen of the 66 patients who recovered received streptomycin alone, the others received, in addition, various combinations of sulfonamides, penicillin and antiserum. The average daily dose of streptomycin was 0.5 gm intramuscularly and 60 mg intrathecally.

Several authors^{57, 70, 75, 80, 81, 119, 203, 204, 206, 218, 219, 225, 227, 231, 232} have reported cases of *H. influenzae* meningitis that were treated with streptomycin, and many of these cases were probably included among the 100 mentioned above. Analysis of the individual reports, however, yields valuable information. When streptomycin therapy alone was instituted early in the course of the disease and in adequate amounts, the results were almost uniformly favorable.^{80, 203} When the treatment was begun late in the disease, the results were quite irregular. The findings indicate that streptomycin alone, in adequate doses intramuscularly and intrathecally, is effective if the treatment is begun early in the course of the disease, sulfadiazine and antiserum should also be used when treatment is started late. The

streptomycin should be given for at least seven days.²¹³

The development of streptomycin-resistant strains of *H. influenzae* has been noted in 4 cases during the course of treatment.^{80, 119, 203} This untoward phenomenon should be looked for at the first sign of a recrudescence of clinical symptoms and signs or when *H. influenzae* reappears in the cerebrospinal fluid. Sulfadiazine and specific rabbit antiserum should then be added to the therapeutic regime. The occurrence of secondary infections during streptomycin treatment must be watched for constantly and treated vigorously as soon as recognized. Complicating staphylococcal infections were reported in 3 children under streptomycin treatment for *H. influenzae* meningitis.²⁰⁴ One of them died of staphylococcal pneumonia, despite added penicillin therapy, the second had an acute otitis media, and the third had a meningitis due to a staphylococcus, and both responded favorably to penicillin.

Meningitis Due to Miscellaneous Gram-Negative Bacilli

There are reports of streptomycin treatment in cases of meningitis due to the following gram-negative bacilli: *Aerobacter aerogenes*,²²⁵ *Alcaligenes faecalis*,²⁰² *Escherichia coli*,^{202, 218, 220, 225, 226} *Proteus morganii*,^{81, 202} *Pr. vulgaris*,²²⁵ *Klebsiella pneumoniae*,^{202, 224} *Salmonella choleraesuis*,^{202, 225} *Pseudomonas aeruginosa*,^{81, 206, 225} and an achromobacterium.²⁰⁶ The over-all mortality rate in these cases was high, but inspection of the data shows that when streptomycin therapy was instituted early in the course of the disease and given intrathecally as well as parenterally in adequate doses, the results were favorable. Infections of the central nervous system by gram-negative bacilli respond poorly to sulfonamides and little if at all to penicillin. The early and proper use of streptomycin in such cases may therefore be life saving.

Brain Abscess

Of 4 cases treated in Army hospitals, 3 patients improved, but only when parenteral streptomycin therapy was supplemented by drainage of the abscess and local instillation of streptomycin. Both gram-negative bacilli and gram-positive cocci were cultured in these cases.²²⁵ Improvement was noted in an additional case.²⁰²

INFECTIONS OF THE RESPIRATORY TRACT

Acute Infections

H. influenzae and *K. pneumoniae* are the only gram-negative bacilli—except in cases of tularemia, plague and glanders—that are important causes of primary acute pulmonary infections. Such infections are infrequent in adults, are usually superimposed on a chronic bronchiectasis or chronic bronchitis and generally respond poorly to sulfon-

amide or penicillin treatment. Infections due to *H influenzae* may be frequent and serious in infants and children. Several streptomycin-treated cases due to these organisms have been reported^{74-76, 202, 203, 213, 216-218}. A few cases of acute pneumonitis, apparently due to *H influenzae*, responded favorably to streptomycin after failing to improve on sulfonamides and penicillin.^{82, 209, 218} The institution of streptomycin therapy in these patients was followed by prompt clinical improvement and disappearance of *H influenzae* from the sputum.

Pneumonia due to Friedländer bacillus has a high mortality rate²¹⁹ that has not been strikingly influenced by sulfonamides or penicillin. The response to streptomycin in such cases has not been uniformly favorable,^{74, 82, 202, 218, 240} in spite of the fact that the causative organism, *K pneumoniae*, is usually quite sensitive to the drug. The results are readily understandable when one considers the pathology of this disease, which is marked by the early development of multiple pulmonary cavities filled with viscid exudate. Four cases of pneumonia due to Friedländer bacillus have been reported in which streptomycin therapy begun after several days of ineffective sulfonamide or penicillin therapy, or both, resulted in prompt improvement.^{203-205, 211, 217} One case is reported in which a resistant strain of *K pneumoniae* developed in the sputum after two days of streptomycin therapy, the patient nevertheless improved promptly and eventually recovered.⁸² In view of the high mortality in pneumonia due to Friedländer bacillus, the prompt institution of large doses of streptomycin — preferably 10 gm every four hours in adults — seems indicated.

In a case of severe pharyngitis apparently due to *Ps aeruginosa* in a child with leukemia, the organisms quickly disappeared from the throat following institution of streptomycin therapy.²⁰²

Chronic Infections

Chronic bronchiectasis is a distressing and debilitating disease. Treatment of such cases with penicillin aerosol in conjunction with postural drainage has proved to be of much help in reducing the amount of sputum, decreasing the incidence and severity of the episodes of superimposed pneumonitis and in preparing the patients for operations.²⁴¹ Penicillin, however, eliminates only the penicillin-sensitive organisms, and in some patients the infection persists, owing to the presence of the penicillin-insensitive organisms, mostly gram-negative bacilli. The response of such cases to streptomycin has been encouraging.^{82, 208, 209, 218} The volume of sputum diminishes, and gram-negative bacilli disappear promptly following inhalations of streptomycin aerosol.²⁰⁸ The total daily dose of nebulized streptomycin used in some of these cases was 0.5 gm. in 20 cc of saline solution daily.²⁰⁸ Similar cases have been treated by daily intratracheal instillations of 5 cc of streptomycin solution contain-

ing 10 mg per cubic centimeter, with similar favorable results.²⁰⁹

The ease of administration of antibiotics by aerosol offers a simple but often effective means of treating patients with chronic bronchiectasis and chronic bronchitis. Whether or not concomitant parenteral therapy in these patients is advantageous has not been determined, and the problem of development of resistance by the organisms under aerosol treatment must be investigated further.⁸² The rational aerosol treatment of chronic bronchiectasis may well involve the combined use of penicillin and streptomycin.²⁰⁸ Such treatment is probably only palliative but may offer considerable relief from the distressing symptoms, lessen the frequency of complications and possibly arrest the progress of the disease.

Empyema

Several cases of empyema thoracis have been treated with variable results. Details in these cases are lacking.^{202, 216}

Nasal and Sinus Infections

A case of chronic sinusitis due to *K pneumoniae*²¹⁷ was treated with 100 mg of streptomycin aerosol five times daily given by the method of Barach and his associates.²⁴² The patient had undergone two episodes of pneumonia due to Friedländer bacillus during the previous two years. The Friedländer bacilli were promptly eliminated from the nose and sputum. Four patients with ozena possibly due to *K pneumoniae* were treated by parenteral streptomycin, with symptomatic improvement.²⁴³

BACTERIAL ENDOCARDITIS

There are few reports on the use of streptomycin in bacterial endocarditis. Although endocarditis due to gram-negative bacilli is infrequent, the early use of streptomycin in such cases seems indicated. The only reported recovery occurred in a case of subacute bacterial endocarditis due to an unidentified gram-negative bacillus.²⁴⁴ Streptomycin therapy was started in that case after several days of treatment with penicillin and sulfadiazine. Although cultures had already become negative, it was thought that the streptomycin helped effect the cure.

The usefulness of streptomycin in endocarditis, however, may not be limited to infections with gram-negative bacilli. Indeed, the drug may be superior to penicillin in certain infections, such as those due to enterococci and nonhemolytic or alpha-hemolytic streptococci, that are resistant to the concentrations of penicillin maintained in the blood but sensitive to those attainable with streptomycin. Three cases of subacute bacterial endocarditis caused by such organisms were reported.¹²² Two of them were due to nonhemolytic streptococci that were inhibited by 1 unit of streptomycin but required 6 units of penicillin in one case and 4 units in the other. Treatment with streptomycin was

successful in the first case after five weeks of penicillin had proved ineffective. The second case was also treated with streptomycin after an unsuccessful course of penicillin. Blood cultures in this case were negative during streptomycin therapy, and the patient eventually recovered despite two positive blood cultures obtained after the streptomycin had been stopped. In the third case the organism was a strain of *Streptococcus viridans* that was inhibited by 0.8 units of penicillin and 0.1 units of streptomycin per cubic centimeter. Penicillin had produced no effect in this case. The patient died after five days of streptomycin treatment, but at autopsy no bacteria were found in the vegetations on the heart valves. In these 3 patients the dosage of streptomycin was small—only 0.5 gm a day. A fourth case, due to *Str. faecalis*, was treated unsuccessfully.^{245, 246}

In cases of subacute bacterial endocarditis due to gram-positive cocci that do not seem to respond to penicillin, the sensitivity of the organism to both penicillin and streptomycin should be determined if possible, and streptomycin treatment instituted if the organism is found to be insensitive to penicillin but sensitive to streptomycin. The dose in such cases should be large, preferably about 1.0 gm intramuscularly every four hours for adults.

ENTERIC INFECTIONS

Typhoid Fever

Streptomycin has not been particularly effective in the treatment of typhoid fever or of typhoid carriers. Fifty-one cases of typhoid fever were included in the report of the Committee on Chemotherapeutics and Other Agents.²⁰² The majority of these patients received 4.0 gm of streptomycin daily for seven or eight days without a favorable effect on the course of the disease. Combined oral and intramuscular therapy was used in 15 cases, with results that were no better than those in the cases treated by intramuscular injections alone. Others^{70, 84, 203-213, 218, 225, 240, 247, 248} have reported similar results. Oral and intramuscular streptomycin was ineffective in clearing up typhoid carriers.^{183, 248}

A case in an eighteen-year-old girl²⁴⁹ is worth citing. Treatment was begun on the twenty-seventh day of illness with 1.0 gm intramuscularly every four hours. This was increased to 1.5 gm every four hours after six days and then to 2.0 gm every four hours after another five days, and the latter dosage was continued until the patient died on the fortieth day. During the last five days of life, 3.0 gm of streptomycin was also given orally each day. Blood cultures eventually became negative, but stool cultures remained positive for *Escherichia typhosa* during this treatment. *Esch. coli*, however, disappeared from the stool cultures during this period. Strains of *E. typhosa* obtained from the stool and blood after eight days of therapy were

sensitive to 16 units. At autopsy, typhoid bacilli were grown from the blood, intestinal ulcers, urine and bile. The patient died despite intensive therapy, although the infection was due to an organism that was moderately sensitive in vitro.

Salmonella Infections

Streptomycin therapy of *Salmonella* infections has also been generally unsuccessful,^{70, 145, 202, 243, 250} although some cases may have been favorably influenced.^{202, 250} In 26 collected cases 10 patients recovered during treatment, 2 improved during treatment and later recovered, 6 showed no improvement and 8 died.²⁰² The treatment of enteritis due to *S. typhimurium* in 5 newborn infants has been reported.¹⁴⁵ Streptomycin was given orally to 4 and both orally and intramuscularly to 1 patient. There was little noticeable effect on the clinical course. The normal fecal flora and the pathogens were suppressed by oral doses of 25 to 100 mg every three hours for four days. The organisms reappeared promptly after the end of treatment. No increase occurred in the resistance of the organisms. Further trials of streptomycin with early and prolonged use of large parenteral and oral doses may be indicated in these infections.

Shigella Infections

In a case of bacillary dysentery due to *Shigella sonnei* streptomycin was given by mouth in doses of 1.0 gm five times daily for four days. The diarrhea and fever subsided in twelve hours, and the causative organisms disappeared promptly from the stools.²⁰³ This seemed to be a dramatic response to oral streptomycin alone. Two additional patients with bacillary dysentery due to *Shigella* responded promptly to streptomycin treatment, and stool cultures became negative.²⁰² Prolonged sulfonamide therapy had previously been ineffective in these cases. A prompt response was reported in 5 other cases.²²⁵

Cholera

In 8 Chinese patients suffering from cholera who were treated with streptomycin in doses of 4 gm daily by mouth supplemented by an occasional intravenous dose, there was little indication that the streptomycin offered any clinical advantages over the use of hydration or sulfonamides, or both.¹⁴⁴ The number of cholera organisms in the stools was apparently reduced promptly and markedly following oral streptomycin, although some were still present by culture and their resistance to streptomycin had increased from 5 to 500 units.

BILIARY-TRACT DISEASE

There are reports of 5 cases of cholangitis, with or without cholecystitis, and 2 cases of liver abscess treated with streptomycin, in all of which the patients improved.²⁰² A patient with cholecystitis

improved with streptomycin, but only after cholecystectomy.²⁵ In a case of liver abscess due to an anaerobic hemolytic streptococcus the patient improved, also after surgical drainage.²⁵ Observations on the excretion of streptomycin in such cases indicate that, for the drug to be effective in cholecystitis or cholangitis, it is necessary that liver function be unimpaired and biliary drainage be free.²⁵

PERITONITIS

The reported results of streptomycin therapy in peritonitis are quite variable, as might be expected. Controlled observations in animals and some highly favorable clinical results suggest that it may be of value in cases of peritonitis due to susceptible organisms. In dogs, the mortality from experimental peritonitis was reduced from 70 per cent in controls to 40 per cent in subjects treated with streptomycin.⁸³ In another study, however, better results were obtained in dogs with the use of penicillin and sulfonamides than with streptomycin.⁸⁴ In a collected series of 53 human cases of peritonitis of varied etiology, there were 39 recoveries, 12 deaths and 2 cases in which there was no effect. Most of these patients received 1 or 2 gm daily for eight days, and more than half of those who recovered also received other forms of chemotherapy. In this series there were only 3 deaths in 21 cases complicating appendicitis.²⁰²

No spectacular effects were reported from streptomycin on the course of peritonitis in 12 patients, most of whom also received penicillin in what may now be considered small doses. There was only 1 death among 7 cases in which the peritonitis was secondary to appendicitis, and 1 death in 5 cases that were secondary to perforated peptic ulcers. Coliform organisms were most frequent in cultures of the former, and alpha-hemolytic streptococci predominated in the latter.⁷⁴ In Army hospitals, about 80 per cent of the streptomycin-treated cases of peritonitis recovered, but the infection had already been localized in half the cases when the streptomycin therapy was started.²²⁵

A prompt response to streptomycin was noted in 2 isolated cases, one due to a colon bacillus²²¹ and the other to *Ps. aeruginosa*.²⁰³ A third case of peritonitis associated with a ruptured appendix was treated successfully with streptomycin in conjunction with appendectomy and surgical drainage.²²⁴ Good results were also noted from streptomycin given prophylactically to 2 patients in whom the peritoneum was accidentally contaminated during an operation.⁷⁴

Streptomycin may be useful as a prophylactic agent in the preparation of patients for large-bowel surgery because of the marked reduction in the intestinal flora that follows its oral administration. This reduction is usually greater than that following

succinylsulfathiazole,⁸⁶ but occasionally it may not occur.²¹⁷

The optimum treatment of peritonitis may involve the simultaneous use of large doses of both penicillin²³² and streptomycin, with the realization that in the presence of pocketed collections of pus the response to therapy may be slow but that complications may be avoided and the eventual duration of the disease shortened.

INFECTIONS OF THE EYE

Good results were reported in 9 patients with corneal ulcers treated by streptomycin solutions placed on the conjunctiva.²¹¹ There were no bacteriologic reports in these cases, but gram-negative bacilli may cause such infections.²³⁴ One patient²¹⁰ with a severe corneal ulcer due to *Esch. coli* responded quickly to streptomycin after treatment with penicillin intramuscularly and locally and with sulfadiazine by mouth had failed.

INFECTIONS OF THE EAR

There are few reports on the streptomycin treatment of infections of the ear. One report includes 8 cases of otitis media, with improvement in 7 and no effect in 1.²⁰² A child with otitis media and mastoiditis due to *Ps. aeruginosa* failed to respond to streptomycin.²⁰³

Streptomycin has been used locally in 27 cases of suppurative ear infections that were mainly due to chronic otitis media.²²¹ Streptomycin preparations containing 1 to 20 mg per cubic centimeter of physiologic saline solution were instilled four times daily for one to seven weeks. Drainage stopped during treatment and did not recur during follow-up periods of one to four months in about half the cases. In the others the discharge persisted or recurred after temporary improvement. Changes in the bacterial flora were frequent, and streptomycin-resistant strains developed in many of the cases during treatment.

Otitis externa was treated with wicks saturated with streptomycin solutions of 2.5 to 5 mg per cubic centimeter in 6 cases, 5 patients improved and 1 with insensitive organisms was unimproved.²²⁵ In 3 cases of mastoiditis, 2 patients were improved and 1 unaffected by streptomycin, but all 3 required surgery.²²⁵

INFECTIONS OF SKIN, WOUNDS AND BONES

Streptomycin solutions, in the form of 2 to 5 mg per cubic centimeter on wet dressings, were applied directly to sloughing or granulating wounds of 4 patients with burns or avulsions.⁷⁴ All improved, granulations became red and healthy, and grafts took well. The bacterial flora, however, did not change, except that the resistance of some of the organisms to streptomycin increased markedly. In 19 patients with infections of the skin, 11 improved and 8 showed no effect from streptomycin given

intramuscularly or, in some cases, topically.²⁰² Six patients with operative-wound infections also improved.²⁰² Streptomycin in a base of carbowax and propylene glycol was found helpful in several cases of persistent infections of the skin around the anus.⁸⁶

In Army hospitals 179 patients with wound infections were treated, with improvement in 72, no improvement in 105 and death in 2.²²⁵ Improvement usually coincided with adequate revision of the wounds, and streptomycin was considered useful only as an adjunct to surgery. One patient with pemphigus was unimproved, whereas 1 case each of generalized furunculosis and acneiform ulcerations improved after neither had responded to penicillin.

Topical streptomycin has been considered superior to penicillin in experimental wound infections because of its wider range of activity under such conditions.¹⁸⁴

Osteomyelitis

Streptomycin may be useful in cases of osteomyelitis in which susceptible gram-negative bacilli predominate, but it seems to be of value mainly as an adjunct to adequate surgery.^{74 254 255} Improvement has been noted in 11 of 15 reported cases.^{74 202, 254, 255} One fatal case due to widespread infection followed the gradual development of resistance by the causative organism, *A. cloacae*.²⁵⁴ In some cases, healing continued despite the development of resistant strains, suggesting that the surgery was an important part of the therapy.²⁵⁵

TUBERCULOSIS

The most extensive studies on the use of streptomycin in clinical tuberculosis thus far reported are those of Hinshaw and his collaborators.^{205 256} They had previously satisfied themselves that this antibiotic was distinctly superior to the sulfones (Promin, Diasone and Promizole) in the treatment of experimental tuberculosis in guinea pigs.^{126 155 156} Another series of cases is under close study by Dr Walsh McDermott at the New York Hospital,²⁰² and isolated cases of tuberculous meningitis have been reported from other clinics.^{70 84 257-260} The report of the National Research Council²⁰² summarized the findings in 87 of these cases. A group of 15 cases was also reported from Army hospitals.²²⁵ A considerable experience is also being accumulated in Veterans Administration hospitals.²⁵¹

Miliary Tuberculosis

The report of the National Research Council²⁰² mentions 7 patients with miliary tuberculosis, all of whom showed regression of the pulmonary lesions on x-ray examination and reduction of fever and systemic signs of infection during streptomycin therapy. Improvement was usually observed within

the first two or three weeks. Three of these patients died, however, and meningitis was observed at autopsy. Of special interest are 2 patients who developed signs of meningitis while receiving intramuscular streptomycin, the meningitis apparently responded after the drug was also given intrathecally. The importance of early diagnosis and persistent treatment with maximum tolerated doses parenterally has been stressed.²⁰⁵ Clinical, x-ray and histopathologic evidences of healing trends have been observed, but no actual cures are as yet reported.²⁰⁵

Tuberculous Meningitis

The results of intensive treatment both intramuscularly and intrathecally for at least four months in this highly fatal disease are somewhat encouraging regarding the possibility of producing arrest of the infection. Parenteral therapy alone appears to be inadequate. The cerebrospinal fluid usually continues to show elevated protein and cell counts, although the values for sugar may become normal after therapy. Serious sequelae, however, have been observed among most of the survivors. The 4 survivors among the 7 patients treated by Hinshaw and his co-workers²⁰⁵ had received intrathecal therapy, — the 3 patients who died had not, — and all had some form of residual neurologic disturbances, thus, one was blind, probably owing to retrobulbar neuritis, one was deaf, possibly as a result of the toxic effects of the streptomycin, the third had profound disturbances of cerebellar function and some mental retardation, and the fourth had paralysis of one of the ocular muscles. In 9 cases reported by others^{70 84 225 257-260} 3 patients recovered, with apparent improvement in the neurologic findings, and the other 6 died.

Pulmonary Tuberculosis

The cases reported were selected chiefly from among those with positive sputums and far advanced or moderately advanced lesions that would be expected to advance under conventional treatment. Streptomycin was given for two to six months in doses of 1 to 3 gm daily. No progression of the disease was noted clinically or on x-ray study in any of the cases during therapy, and even the fatal cases showed some subjective improvement.²⁰⁵ X-ray improvement and negative sputums during treatment were noted in two thirds of the cases, a similar proportion of those with cavities showed closure of these cavities. Reactivation occurred a month after the treatment had been discontinued in 6 of a group of 32 cases, in 3 of which the patients were given a second course, 2 then improved, whereas the third had a rapid progression to a fatal outcome associated with a streptomycin-resistant strain of *Mycobacterium tuberculosis*. There were 4 other deaths, all in far advanced cases.²⁰⁵ In 4 cases treated in Army hospitals, 3 patients were unim-

proved, and 1 with pneumonia was markedly improved²²

Only 4 cases of early infiltrative pulmonary tuberculosis treated with streptomycin have been reported²² These were all in young children with proved tuberculosis On a dosage of 1 gm daily for twenty or thirty days there was clinical and roentgenologic improvement The patients had remained well during a follow-up period of two or three months

Streptomycin may have contributed to the recovery of 7 patients treated with radical surgery for pulmonary tuberculosis²⁰⁵

Renal Tuberculosis

Streptomycin was not considered curative in renal tuberculosis, and bacilluria tended to recur in the advanced cases²⁰⁵ Six out of 14 patients obtained only temporary subjective relief and 8 had a reduction or disappearance of tubercle bacilli from the urine by direct smear^{202 225 263} Only 2, however, had consistently negative guinea-pig tests for prolonged periods In another group of 7 cases, 2 patients were improved and 5 were unimproved²²⁵

Miscellaneous Forms

Six patients with visible ulcerating tuberculous lesions of the upper respiratory tract, trachea and bronchi were treated with streptomycin, all showed healing of the lesions within three to six weeks^{202 225 264} Only 1 of 8 patients with tuberculous empyema showed improvement despite intrapleural injections, with or without intramuscular treatment²⁰² Cutaneous tuberculous fistulas were treated in 15 cases, in 10 of which the fistula closed during therapy and had remained closed for four to ten months²⁰⁵ Prompt healing of a chronic tuberculous sinus in 1 patient occurred with streptomycin therapy²⁶⁵ Three patients with tuberculous peritonitis showed clinical improvement²⁰⁵ Four of 5 patients with tuberculosis of the bones and joints improved under treatment with streptomycin²⁰⁵ Only 1 of 4 patients with lupus vulgaris improved^{205 225}

Histologic Studies

Pathological changes have been studied in 5 patients who died following treatment for tuberculosis with streptomycin over periods of several weeks or longer²⁶⁶ The tuberculous lesions of the spleen, liver and particularly the lungs seemed to be more discrete and less cellular than those seen in untreated cases Many of the lesions were atrophic, fibrotic and hyalinized and showed a minimum of caseation Meningeal lesions were absent in some patients in whose cerebrospinal fluid tubercle bacilli had previously been demonstrated

The consensus regarding the role of streptomycin in the treatment of tuberculosis in human beings is that it exerts a palliative effect by producing

some degree of bacteriostasis The immediate results have been most striking in miliary, meningeal and laryngeal tuberculosis²⁰² The disease requires large doses — about 3 gm daily in adults — for prolonged periods, and treatment should not be undertaken unless adequate amounts of streptomycin are available to permit continuous therapy for at least two to four months It is generally agreed that streptomycin cannot be regarded as a substitute for present methods of sanatorium and surgical therapy^{205 267} Further study of the entire problem of streptomycin therapy in tuberculosis is being sponsored by the American Trudeau Society, the medical section of the National Tuberculosis Association²⁶⁷

TULAREMIA

Streptomycin is particularly efficacious in the treatment of acute tularemia^{202 203 207 225 227 240 — 265-277} It seems to be equally effective against all the acute forms that have been treated — ulceroglandular, typhoidal and pulmonary A comparative study of the treatment of tularemia with immune serum, hyperimmune serum and streptomycin indicates that streptomycin is the therapy of choice in desperately ill patients and that only streptomycin or hyperimmune serum reduces the mean duration of the disease to less than two and a half months if treatment is begun later than the second week of the disease²⁷¹

The report of the Committee on Chemotherapeutics and Other Agents²⁰² includes 67 cases of all types of tularemia, with recovery in 63 There was pulmonary involvement in 11, and the majority of these patients had previously received sulfonamide and penicillin therapy without effect The average dose was only about 10 gm daily for a period of seven days

A series of 11 cases of tularemic pneumonia and 1 case of tularemic pleurisy has been reported in which all the patients showed a prompt clinical response to 0.4 to 1.6 gm daily for six to fourteen days Most of them received 0.5 or 0.6 gm a day for six or seven days One of the patients died suddenly on the seventh day of treatment, presumably of a massive pulmonary embolus the temperature had been normal for four days, and the pulmonary lesion had been regressing *Pasteurella tularensis* disappeared rapidly from the sputum or pleural fluid in all cases It was believed that healing of the pulmonary lesions and the primary ulcers was accelerated, but clinical recovery occurred even more promptly Serum agglutinin titers rose in all cases after treatment, and this rise was marked and rapid in some cases The results were considered to justify a clinical therapeutic trial of streptomycin in doses of 1 to 2 gm daily in cases of severe pneumonia of undetermined etiology occurring where tularemia is endemic²⁷⁷

Three patients were treated with streptomycin because of the persistence of easy fatigability, malaise and intermittent fever several months after an episode of acute tularemia.²⁷⁵ These patients, who were possibly suffering from chronic tularemia infection, showed no improvement in their symptoms and signs

BRUCELLOSIS

Streptomycin has not proved to be of great value in the treatment of brucellosis. Reports of 77 cases, mostly acute infections, are available.^{62, 84, 202, 203, 218, 243, 278-280} Blood cultures were usually negative during treatment, but bacteremia often recurred after therapy had been stopped, and in 1 case persisted during and after the treatment.²⁰³ The effect on the relapse rate remains to be determined, but 2 cases have been reported in which evidence of chronic brucellosis persisted during a follow-up period of one and a half to two years.²⁸¹ The development of a markedly resistant strain of *Br. abortus* occurred during streptomycin treatment in one case of chronic brucellosis.⁶² The possibility of better effects from a combination of sulfadiazine and streptomycin is suggested from results in 2 cases.²⁷⁹

MISCELLANEOUS INFECTIONS

Streptomycin was used in a group of 9 cases of chronic urethritis due to *Neisseria gonorrhoeae* that were clinically resistant to sulfonamide and penicillin therapy.²⁸² 7 cases cleared promptly after a short course of streptomycin consisting of six intramuscular injections of 0.5 gm each. One of the patients, who had prostatic involvement, improved clinically but was not cured, in another, who had chronic epididymitis, smears of the urethral discharge became negative, but the epididymitis did not clear. In another group of 4 previously untreated cases, streptomycin produced a favorable response.²⁸³ Streptomycin is probably indicated for the occasional cases of gonorrhea that prove resistant to sulfonamides and penicillin.

No published reports are available on the use of streptomycin in clinical cases of pertussis. Bradford²¹² found that streptomycin in nose drops (10 mg per cubic centimeter, five drops in each nostril every three hours) or used as an aerosol for three days was effective in eliminating *H. pertussis* from throat cultures. After intramuscular injections negative cultures were not obtained so rapidly as after the local applications.

Malleomyces mallei was eliminated by streptomycin treatment from the skin ulcers of a patient with osseous tuberculosis and secondary glanders.²⁰³

Streptomycin is somewhat effective in experimental spirochetal infections in animals, as noted above in Part I. In a clinical study streptomycin was given in small doses over a ten-day period to

3 patients with early syphilis and to 1 with a gummatous lesion, all improved but later relapsed.²¹⁰

No reports have been found on the use of streptomycin in human viral infections. In 2 patients with typhus fever streptomycin had no effect.²⁰²

One patient with acute pulmonary moniliasis,⁷¹ 1 with blastomycosis of the skin and 1 with a *Cryptococcus hominis* meningitis were treated with streptomycin without effect.²²⁶ No reports are available on the use of the antifungal antibiotic derived from cultures of *Streptomyces griseus* in the treatment of human cases.^{7, 8}

A case of human amebic hepatitis was treated ineffectively with streptomycin.²⁰²

DISEASES OF UNCERTAIN ETIOLOGY

Streptomycin has been used in 29 cases of ulcerative colitis,^{86, 202, 226, 284, 285} with dramatic improvement in only 2 cases,^{284, 285} temporary improvement in 6 and failure to arrest the disease in the remaining 21. In some acute exacerbations the drug sometimes lowered the temperature and seemed to avert a fatal outcome.⁸⁶ No beneficial effect from streptomycin was observed in 6 cases of rheumatoid arthritis,²⁰² 1 case of infectious mononucleosis,²⁰² 1 case of relapsing febrile panniculitis (Weber-Christian's syndrome),²⁰³ 1 case of Hodgkin's disease,²²⁶ and 1 case of Reiter's syndrome.²⁰² Six patients with nonspecific urethritis were treated with streptomycin, 2 were improved, and the remainder were unimproved after several days of therapy.²⁸² Dienes and Kane²⁸⁶ found streptomycin to be of value in some cases of genitourinary infections in which cultures yielded pleuropneumonia-like organisms. They also observed suggestive effects on the course of the disease in cases of Reiter's syndrome. In 13 infants with epidemic diarrhea of undetermined etiology treated with oral streptomycin alone, 10 improved, and 3 died, in at least 4 of these cases survival was attributed to the streptomycin.²²⁶ The drug seemed beneficial in a case of pylethrombophlebitis.²⁸⁷

TOXIC EFFECTS

Although most patients tolerated streptomycin quite well, the drug is not nearly so free of untoward effects as penicillin. Both local and constitutional reactions are frequent, but none have been reported thus far following ingestion, inhalation or local applications to skin and wounds.

Local Reactions

Pain, tenderness and induration at the site of intramuscular injections are quite frequent and are often accompanied by local redness and heat.²⁰² These manifestations may be more frequent and severer with subcutaneous injections. The incorporation of procaine hydrochloride may lessen the discomfort that follows within a few minutes after the injection, but the immediate discomfort may

be minimized if the volume of injected material is kept to a minimum. The use of "pure" crystalline streptomycin sulfate is said to produce only minimal discomfort at the site of injection.²⁰²

In the treatment of meningitis in human beings, intrathecal injections of streptomycin have been attended by few untoward effects, in contrast to the reactions noted in experimental animals.^{155 156} Severe reactions were observed in 5 patients immediately or within nine hours after the first intrathecal or intraventricular injection of 2500 to 100,000 units of streptomycin in concentrations of 10,000 to 20,000 units per cubic centimeter.²⁰⁶ These reactions were characterized by coma and changes in pulse, temperature and respiration. Death from respiratory failure occurred in 2 cases. Since all patients had meningitis, the deaths were not necessarily related to the injections of streptomycin. Early and probably impure lots were used in these cases. Streptomycin given by these routes to many patients with meningitis has been followed by much benefit, without these alarming reactions.^{50 51 119 204}

An increase in meningeal signs or pleocytosis in the cerebrospinal fluid, or both, has been observed.^{7 51 119 206} Fever and pleocytosis may persist in patients recovering from meningitis who are receiving intrathecal streptomycin, but these signs promptly subside when the intrathecal injections are stopped.⁵¹ Even in subjects without meningitis the cerebrospinal fluid may contain 180 to 1500 white cells per cubic millimeter, mostly polymorphonuclears, twenty-four hours after the intrathecal injection of 10 to 20 mg of streptomycin.⁷² These mild reactions should not discourage the use of streptomycin by this route, since the drug is such an important part of the treatment of meningitis.

Constitutional Reactions

Headache, flushing of the skin, nausea, vomiting, a fall in blood pressure and occasionally convulsions were observed immediately following injection of some of the earlier lots of streptomycin.^{69 71 86 202 253} This type of reaction, which is due to a histamine-like impurity in the streptomycin,^{27 289} may be avoided by the use of benadryl,¹⁸³ and probably with pyribenzamine, although the use of the latter has not been reported. Two deaths have been ascribed to this type of reaction following injections of streptomycin.²⁹⁰ Recent lots of streptomycin are relatively free from the histamine-like substance.^{27 202}

Skin eruptions and fever may appear, together or separately, usually between the third and tenth days of streptomycin treatment. The skin lesions may be erythematous, urticarial, maculopapular or hemorrhagic.* Such reactions may recur on subsequent administration. Eosinophilia has been noted with and without the skin rash. Myalgias and arthralgias were noted, especially with some of the earlier batches of streptomycin.^{71 72 85 255} Strepto-

mycin should usually be discontinued if these reactions appear.²⁰²

Probably the most striking untoward effect of streptomycin has been the disturbance of function of the eighth cranial nerve, apparently without relation to the injection of streptomycin into the central nervous system. This effect has been noted with both early and recent batches of streptomycin, suggesting that the effect is not due to an impurity but perhaps represents a selective neurotoxic action of the drug.^{27 289} The incidence of this type of reaction in human beings varies. Only 2 cases of vestibular disturbance were recognized among 706 patients treated in Army hospitals.²²⁵ Absence of vestibular response was noted in 3 of another series of 81 streptomycin-treated patients after average doses of 0.5 gm intramuscularly every four hours for a total of 10 to 50 gm.¹⁸¹ These 3 had complained of dizziness during treatment. The patients treated ranged in age from nineteen to fifty-one years, and those with known ear disease or meningitis were excluded. An additional patient in this group manifested a severe loss of hearing two weeks after treatment but later improved.

Symptoms of eighth-nerve difficulty were reported in 23 cases among those treated at the Mayo Clinic.¹⁵⁰ No patients complained of true objective or subjective vertigo, but they experienced dizziness, light-headedness or giddiness; these symptoms were first noted on change of position. Most of the patients had a positive Romberg test, the imbalance varied from a gentle swaying in all directions to falling in any direction. The patients usually could not walk unassisted. Spontaneous nystagmus, which was noted in 1 patient on change of position, disappeared forty-eight hours after the streptomycin had been stopped. Five of the 23 patients had some loss of hearing, 4 of these 5, however, had tuberculous meningitis. Loss of hearing was noted with daily doses of 3 to 10 gm, but not with 1 or 2 gm. Tinnitus preceded the loss of hearing in all 5 cases. In 3 cases the hearing improved when the streptomycin was stopped or the dose decreased, and in 1 case, deafness recurred when streptomycin was reinstituted. It was therefore believed that streptomycin affected the cochlear apparatus and produced temporary deafness. The loss of vestibular response as judged by caloric and rotation tests has persisted in most of the patients. The patients compensate for this defect, however, by other postural mechanisms so that the symptoms usually persist only for one to three months.^{180 202}

Davenport²⁵¹ reported 90 per cent incidence of vestibular changes in patients treated with streptomycin for tuberculosis, and varying degrees of deafness resulted in a small number of cases.

Toxic effects of streptomycin on the kidneys and livers of experimental animals were described in Part I. No effects on liver or kidney function were noted after single doses of 600 mg intravenously in

*Davenport noted the occurrence of exfoliative dermatitis in 1 case.

6 subjects, and no latent toxic effects were observed in 100 patients given an average total dose of 12.5 gm over a ten-day period.⁶⁹ Abnormal urinary findings and urinary retention were noted with some early and impure lots of streptomycin.^{183, 186, 288} Hyaline and granular casts were found in the urine of 9 of 10 patients receiving crystalline streptomycin, particularly when the urine was acid.²⁰² There was no evidence of renal impairment,^{69, 71, 288} as judged by urea-clearance tests, blood nonprotein nitrogen determinations and concentration-dilution tests. Effects of streptomycin on the kidneys, as manifested by proteinuria, cylindruria, hematuria, and occasionally azotemia, have been noted in another group of patients, but these effects disappeared on withdrawal of the drug.²²⁵ Two cases of acute nephritis have been noted in patients with typhoid fever under treatment with streptomycin.^{213, 291} The role of streptomycin in these cases is not clear.

A diffuse fatty degeneration of the liver was noted at autopsy of a patient who had received streptomycin therapy for miliary tuberculosis, peritonitis and meningitis, but the cause of the liver changes was not clear.¹⁸⁶ No evidence of impairment of the hematopoietic system has been reported by most observers.^{69, 70, 71, 186, 288} Thrombocytopenic purpura occurred during streptomycin treatment of a case of brucellosis and cleared promptly when the antibiotic was withdrawn.²⁹¹

DEVELOPMENT OF BACTERIAL RESISTANCE DURING TREATMENT

The appearance of resistant strains of bacteria has been noted during streptomycin treatment of urinary-tract infections,^{31, 50, 74, 110, 194, 202, 213, 224-226, 240} respiratory-tract infections,^{82, 192} meningitis,^{80, 119, 203} otitis,²²¹ enteric infections (cholera),¹³⁴ biliary-tract infections,^{110, 240} osteomyelitis,^{74, 264} and infections of the skin and wounds.⁷⁴ A wide variety of bacteria that have been observed to acquire resistance to streptomycin in man during therapy include *A. aerogenes*,^{31, 50, 110, 194, 224} *A. cloacae*,²⁵ *Esch. coli*,^{50, 213, 214, 240} a paracolon bacillus,⁵⁰ *Ps. aeruginosa*,^{31, 50, 110, 255} *Pr. vulgaris* (*B. proteus*),^{194, 226} *K. pneumoniae*,^{50, 82} *H. influenzae*,^{50, 82, 119, 203} *V. comma*,¹³⁴ *Myco. tuberculosis* var *hominis*,^{192, 198, 205} *Staph. aureus* and *Staph. albus*,¹¹⁰ alpha-hemolytic and beta-hemolytic streptococci,¹¹⁰ *Str. faecalis*,^{214, 226} *Br. abortus*⁸² and possibly diphtheroids.¹¹⁰

Theories on the development of resistance were discussed in Part I. Regarding the occurrence of this phenomenon clinically, two possible explanations have been offered: either the original pretreatment bacterial population consists of both resistant and susceptible organisms and exposure to streptomycin eliminates the sensitive strains and allows the resistant ones to flourish or the naturally sensitive strains become adapted to the antibiotic in some manner so that they can multiply in its

presence. Naturally resistant strains, including *Esch. coli*, *Pr. vulgaris*, *Ps. aeruginosa*, alpha-hemolytic streptococci and diphtheroids, have been noted.^{82, 89, 110} The usual methods for determining bacterial sensitivity are such that small numbers of naturally resistant organisms may easily be missed. The occurrence or appearance of resistant strains in man during streptomycin therapy is important because it may seriously interfere with the efficacy of the treatment.

Alkalinization of the urine during streptomycin therapy⁸⁶ may offer a means of limiting the development of resistant strains of organisms in some cases of urinary-tract infection. The use of large initial doses of streptomycin in an attempt to avoid exposure of the organisms to subinhibitory concentrations of the drug seems logical and has been suggested.^{202, 214-216, 228, 289} Yet even when large doses of streptomycin were given initially, resistant strains of bacteria sometimes developed, particularly when the reaction of the urine was acid.⁵⁰

In cases of tuberculosis, resistant strains may not become apparent until after several weeks or months of treatment. Tubercle bacilli obtained from such cases are equally resistant when cultured directly from sputum, urine or gastric aspirations, from such cultures after storage in a refrigerator or when the cultures are made from infected organs of guinea pigs inoculated ten or more weeks previously with material from the patient and when subsequently maintained on glycerine egg agar for several weeks.¹⁹¹ The implications of these observations regarding the possibility of streptomycin therapy in cases of cross-infection or laboratory infection with such strains are obvious.

Just how long resistant strains may persist in the patient once they have appeared during therapy is not known. In some patients treated for chronic urinary-tract infections, such resistant strains were demonstrated for several months⁸⁶ and in 1 case, for as long as eleven months.¹¹⁷

SUMMARY

Streptomycin has proved most effective in acute tularemia and in cases of meningitis due to gram-negative bacilli, especially *Haemophilus influenzae*. It is useful in most gram-negative bacillus infections, particularly those of the urinary and respiratory tracts. The results in some forms of tuberculosis are encouraging, and it is at present the best available chemotherapeutic agent for tuberculous infections. Typhoid fever, *Salmonella* infections and brucellosis have not responded favorably. It may be useful as a second line of defense in some cases of coccal infections that prove insensitive to the sulfonamides and penicillin or develop fastness to these agents.

The greatest limitation to the clinical usefulness of streptomycin is the readiness with which most organisms develop resistance to it.

Streptomycin is relatively nontoxic. The most serious untoward effect that has been noted is a disturbance in vestibular function. This effect has been observed mainly following the use of large amounts of the drug over prolonged periods.

Streptomycin is a valuable addition to the group of agents that are used for the definitive treatment of infectious diseases, particularly since it is effective in some infections that are influenced little, if at all, by other available agents.

REFERENCES

20. Committee on Chemotherapeutics and Other Agents. National Research Council. Streptomycin in treatment of infections: report of one thousand cases. *J A M A* 132:4-11 and 70-76 1946
21. Morgan H. J., and Hunt, J. S. Streptomycin in clinical practice: review and case reports. *Am Practitioner* 1:73-86 1946
22. Weinstein L. Treatment of meningitis due to *Haemophilus influenzae* with streptomycin: report of nine cases. *New Eng J Med* 235:101-111 1946
23. Hinshaw H. C., Feldman, W. H., and Pfuetze K. H. Treatment of tuberculous with streptomycin: summary of observation on one hundred cases. *J A M A* 132:778-782 1946
24. Carr, M., Duthie, E. S., and Smith H. V. Intrathecal streptomycin in meningitis: clinical trial in tuberculous coliform and other infections. *Lancet* 2:153-155, 1946
25. Atwell, R. J., and Smith D. T. Primary tularemia pneumonia treated with streptomycin: report of two cases. *South M J* 39:558-560 1946
26. Ozer, A. M. Streptomycin aerosol in treatment of chronic bronchitis: preliminary report. *Proc Staff Meet., Mayo Clin* 21:53 1946
27. D-rast, T. M., Sokalchuk A. J., Norris C. M., and Brown C. L. Streptomycin therapy in Hemophilus influenzae pulmonary infections. *J A M A* 131:194-196 1946
28. Owers, W. C. Streptomycin treatment of corneal abscess caused by *Escherichia coli*. *Am J Ophthalm* 29:1007-1009 1946
29. Albertstadt, N. F., and Price A. H. Corneal ulcer treated with streptomycin. *Am J Ophthalm* 29:1106-1111, 1946
30. Bradford W. L. Personal communication
31. Keeler C. S., Weinstein L., and Hewitt, W. L. Clinical experience with streptomycin: study of 50 cases. *Tr A Am Physicians* 59:706-719 1946
32. Adcock, J. D., and Plumb R. T. Streptomycin for urinary tract infections. *J A M A* 133:579-584 1947
33. Potter J. E. Discussion of Adcock and Plumb
34. Hirschfeld, J. W. Discussion of Adcock and Plumb
35. Remann, H. Discussion of Keeler, Weinstein, and Hewitt
36. Zappay, W. G., and Carlson H. J. Experiences with streptomycin effectiveness in infections of infants and children. *Clinics* 5:635-645 1946
37. Hays, A. L., Brown R. H., and Drucker, A. P. Influenzal meningitis treated with streptomycin: report of three cases with recoveries. *Arch. Pediat* 63:559-566 1946
38. Shilds, W. P. Meningitis due to *Escherichia coli*: streptomycin therapy. *J A M A* 132:514 1946
39. Harris, H. W., and Finland M. Experiences with streptomycin therapy. *North Carolina M J* (in press)
40. Jacob H. G. Streptomycin in treatment of case of persistent urinary infection. *New York State J Med* 46:883-885 1946
41. Blackmore, B. G., Sommerness M. D., and Scott E. G. Treatment of obstinate case of aerobacter bacilluria with streptomycin. *Delaware State M J* 18:101-104 1946
42. Bordin, A. Jr., Ottenberg D., Dietz, C. C., and Brown C. L. Streptomycin therapy in infections of urinary tract: failure because of development of resistance. *J A M A* 132:634 1946
43. D-Bakey M. E., and Pulaski E. J. Analysis of experience with streptomycin in United States Army hospitals: preliminary report. *Surgery* 20:749-760 1946
44. Ruess, S. L. Present status of streptomycin therapy. *J Urol* 57:79-83 1947
45. Aikawa J. K., Gillman C. M., Herndon E. G., Jr. and Harrell G. T. Simple laboratory aids for control of streptomycin therapy in general practice. *South M J* 40:141-153 1947
46. Pool T. L., and Cook E. N. Present concepts of treatment of infections of urinary tract. *J A M A* 133:584-587 1947
47. Albright, F. Personal communication
48. Kane L., and Foley G. E. Personal communication
49. Butler L. J., Low M. D., and Reinhart J. B. Meningitis due to *Haemophilus influenzae*: report of case treated with sulfadiazine streptomycin and antiserum with recovery. *North Carolina M J* 7:8-12, 1946
50. Newman S., Goodman S., Robinson C., and Ray L. Influenzal meningitis: report of three cases treated with streptomycin and sulfadiazine. *J Pediat* 29:14-19 1946
51. Alexander A. J. Meningitis due to *Escherichia coli* treated with streptomycin. *J A M A* 131:663-665 1946
52. Tanaka S., Grynbaut B., and LeCompte, P. M. Friedländer's meningitis treated with streptomycin. *New Eng J Med* 235:631-633 1946
53. Barce M. *Salmonella meningitis*: report of case treated with streptomycin. *Bull. Charlotte Memorial Hosp* 2:44-47 1946
54. Bishop C. A., and Rasmussen R. F. Klebsiella pneumonia treated with streptomycin. *J A M A* 131:821 1946
55. Learner N., and Minnich W. R. Friedländer pneumonia treated with streptomycin: report of case with prompt recovery. *Ann Int Med* 25:516-520 1946
56. Geier F. M. Case of Friedländer's bacillus pneumonia treated with streptomycin. *Pennacene Foundation M Bull* 4:159-163 1946
57. A Textbook of Medicine by American Authors. Edited by R. L. Cecil 1:665 pp. Philadelphia W. B. Saunders Company 1943. P. 315
58. Nichols D. R., and Herrell W. E. Streptomycin: its clinical uses and limitations. *J A M A* 132:200-205 1946
59. Segal M. S., and Ryder C. M. Penicillin inhalation therapy. *New Eng J Med* 236:132-138 1947
60. Barach A. L., Garthwaite B., Soroka M., and Anderson F. F. Apparatus for introduction of penicillin aerosol into nasal accessory sinuses with case report of patient with chronic sinusitis. *Ann Int Med* 24:97-103 1946
61. Herrell W. E., and Nichols D. R. Clinical use of streptomycin: study of forty-five cases. *Proc Staff Meet., Mayo Clin* 20:449-462 1945
62. Hunter T. H., and Duane R. B. Jr. Subacute bacterial endocarditis due to gram negative organisms. *J A M A* 132:209-211 1946
63. Cady J. B., and Allen W. H. Case of streptococcus fecalis septicemia treated unsuccessfully with streptomycin. *Guthrie Clin Bull* 16:51-53 1946
64. Cady J. B., and Hunter A. L. Streptococcus fecalis septicemia: concluding report of case. *Guthrie Clin. Bull* 16:50-93 1947
65. Goldbloom A. A., Dumanis A. A., and Seidman E. E. P. Streptomycin in typhoid fever: review of current literature and usage. *New York State J Med* 46:1936-1939 1946
66. Pulaski E. J., and Ampacher W. H. Streptomycin therapy in typhoid infections. *Bull U S Army M Dept* 7:101-107 1947
67. Grossman L. A., and Hunt J. S. Typhoid fever: treatment failure with streptomycin. *Am Practitioner* 1:45 1946
68. Flippin, H. F. Cited by Waksman and Schatz
69. Mueller S. R., and Rutenberg A. Use of streptomycin in colon bacillus peritonitis: report of case. *New Eng J Med* 235:327-328 1946
70. Crile G., Jr. Peritonitis of appendiceal origin treated with massive doses of penicillin: report of 50 cases. *Surg Gynec & Obst* 83:150-162 1946
71. Duke-Elder W. S. Diseases of cornea. In *Textbook of Ophthalmology* Vol. 2 2094 pp. St. Louis C. V. Mosby Company, 1944. P. 1915
72. Edwards M. W., and Kirk G. D. Development of resistance to streptomycin by *Arcebuter cloacae*. *Am. J Clin Path.* 16:527-529 1946
73. Lamphier T. A., and Cashman C. Treatment of chronic osteomyelitis with streptomycin: preliminary report. *New Eng J Med* 236:318-321 1947
74. Hinshaw H. C., Feldman W. H., and Pfuetze K. H. Streptomycin in treatment of clinical tuberculosis. *Am Rev Tuberc* 54:191-203 1946
75. Cooke R. E., Dunphy, D. L., and Blake F. G. Streptomycin in tuberculous meningitis: report of its use in one-year-old infant. *Yale J Biol & Med* 18:221-226 1946
76. Thompson J. L., and Wagenheim H. H. Use of streptomycin in acute miliary tuberculosis: report of case. *M Ann District of Columbia* 15:265-270 1946
77. Bornstein P. K. Streptomycin in miliary tuberculosis with tuberculous meningitis: case report with autopsy findings. *Quart. Bull Sea View Hosp* 8:219-227 1946
78. Krafchik, L. L. Tuberculous meningitis treated with streptomycin. *J A M A* 132:375 1946
79. Davenport L. F. Streptomycin in pulmonary tuberculosis. *Bull. New Eng Med Center* 9:83-85 1947
80. Sanford, H. N., and O'Brien D. E. Streptomycin in pulmonary tuberculosis in childhood: results in four children. *J A M A* 133:691-693 1947
81. Cook E. N., Greene L. F., and Hinshaw H. C. Streptomycin in treatment of tuberculosis of urinary tract. *Proc Staff Meet., Mayo Clin* 21:277-280 1946
82. Figs F. A., Hinshaw H. C., and Feldman W. H. Treatment of tuberculosis of larynx with streptomycin: report of case. *Proc Staff Meet., Mayo Clin* 21:127-130 1946
83. Morgan C., and Bosworth D. M. Transpleural rupture of tuberculous spinal abscess treated successfully by streptomycin: report of case. *J Bone & Joint Surg* 28:864-868 1946
84. Baggenstoss A. H., Feldman W. H., and Hinshaw H. C. Effect of streptomycin on histopathology of human tuberculosis. *Am J Path* 22:641 1946. Streptomycin in miliary tuberculosis: its effect on pathological lesions of generalized miliary tuberculosis in human beings. *Am Rev Tuberc* 60:54-76 1947
85. Medical News. Distribution of streptomycin. *J A M A* 132:531 1946
86. Foshay L., and Pasternack, A. B. Streptomycin treatment of tularemia. *J A M A* 130:393-398 1946
87. Abel O. Jr. Use of streptomycin in tularemia. *J Missouri M A* 43:167-169 1946
88. Heather A. J., and Scott, E. G. Tularemia: case treated with streptomycin. *Delaware State M J* 18:148-150 1946
89. Foshay L. Comparative study of treatment of tularemia with immune serum, hyperimmune serum and streptomycin. *Am. J Med* 1:180-188 1946
90. Cohen R. B., and Lasser R. Primary tularemia pneumonia treated with streptomycin. *J A M A* 131:1126 1946
91. Peterson R. L., and Parker R. R. Tularemia pneumonia treated with streptomycin. *Pub Health Rep* 61:1231-1234 1946

- 274 Gordon A M Streptomycin in tularemia *J A M A* 132 21, 1946
- 275 Howe, C, Coriell, L L, Bookwalter, H L, and Ellingson, H V Streptomycin treatment in tularemia *J A M A* 132 195 200, 1946
- 276 Hartnett W G, and Mollica, S G Tularemia treatment of case with streptomycin *Souk M J* 39 774 777 1946
- 277 Hunt J S Pleuropulmonary tularemia observations on 12 cases treated with streptomycin *Ann Int Med* 26 263-276, 1947
- 278 Goetz J R Treatment of undulant fever with streptomycin *Wisconsin M J* 45 496 1946
- 279 Pulaski, E J, and Ampacher, W H Streptomycin therapy in brucellosis *Bull U S Army Med Dept* 7 221 225, 1947
- 280 Howe, C, Miller, E S, Kelly, E H, Bookwalter, H L, and Ellingson, H V Acute brucellosis among laboratory workers *New Eng J Med* 236 741-747, 1947
- 281 Howe, C Personal communication
- 282 Pulaski E J Streptomycin therapy of penicillin resistant and sulfonamide-resistant specific and nonspecific urethritis *J Ven Dis Inform* 28 1 6 1947
- 283 Putnam, L E, Herwick R P, Taggart, S R, and Chinn B D Treatment of gonorrhea with streptomycin preliminary report with cure of four cases *M Ann District of Columbia* 16 14 and 55, 1947
- 284 Kirschner, B Acute fulminating ulcerative colitis treatment with streptomycin *New York State J Med* 46 525 1946
- 285 Lieberman, W Streptomycin treatment of intractable ulcerative colitis *New York State J Med* 46 2178, 1946
- 286 Dienes, L L, and Kane, L W Personal communication
- 287 Wishart, J H, and Peterson, L J Streptomycin therapy in pyelothrombophlebitis *J A M A* 133 539 541, 1947
- 288 Hettig, R A and Adecock, J D Studies on toxicity of streptomycin for man preliminary report *Science* 103 355 357 1946
- 289 Molitor, H Bacterial chemotherapy *Federation Proc* 5 304-312, 1946
- 290 Editorial Streptomycin *J A M A* 130 939 1946
- 291 Sturgis C C Discussion of Keefer, Weinstein, and Hewitt¹¹

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

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CASE 33201

PRESENTATION OF CASE

First admission A fifty-six-year-old housewife entered the hospital complaining of abdominal pain and vomiting

The patient had been in excellent health until two years previously, when she first began to have periodic bouts of nausea and vomiting accompanied by a dull pain in the left upper quadrant. At first the attacks occurred every four or five weeks and lasted for one day. The vomitus was composed of stomach contents with no blood or bile. There was no particular relation to the intake or type of food. During the intervals between attacks she felt well, and the appetite remained normal. After several months, however, she noticed some weight loss. The attacks increased in frequency and severity so that she was admitted to another hospital for study, where a gastrointestinal and a gall-bladder series, as well as a barium enema, were negative. A diagnosis of anemia was made, and liver injections were given for a few months. Nevertheless, she remained unimproved and was forced to eliminate many foods from the diet in an effort to control the pain and vomiting. A "yellow color" developed eighteen months before admission but cleared slowly while iron and weekly injections of liver extract were being given. Then followed a period during which the vomiting and pain subsided, although the patient continued to lose weight. During the following year the attacks recurred, and many studies, including

x-ray films, were done, none of which revealed any abnormality other than anemia. Six months prior to admission the skin became "brownish" for a few weeks. At that time the systolic blood pressure was 86. She was given "injections" and ten salt tablets daily, but after five weeks she became extremely edematous and the treatment was stopped. The attacks of pain grew more frequent and at the time of admission were of daily occurrence. She had limited the food in amount and to soft solids and fluids. Most of the attacks of pain, which were described as dull and nagging, came on after meals, arose in the left upper quadrant and radiated across the abdomen to the right. Although the patient often became extremely hungry, she could eat only a few mouthfuls of food and on several occasions "fainted from hunger." The weight had fallen from 175 to 113 pounds, and the nausea and vomiting had become infrequent. She had gradually become constipated during the second year of the illness so that she required a laxative almost daily. There had been no tarry stools.

Physical examination revealed a well developed but pale and emaciated woman in no acute distress. The skin was dry, with poor turgor. Examination of the heart and lungs was negative. There was considerable spasm of the abdominal wall, with an irregular area of marked tenderness immediately to the left of the umbilicus. No masses were palpated. Pelvic examination was negative.

The temperature was 99.4°F, the pulse 86, and the respirations 20. The blood pressure was 88 systolic, 48 diastolic.

X-ray examination of the chest, as well as an intravenous pyelogram, a Graham test and examinations with a barium meal and enema were negative.

Examination of the blood showed a red-cell count of 2,820,000, with a hemoglobin of 4.6 gm, a hematocrit of 20 and a cell volume of 71 cu microns. A blood smear revealed a marked achromia with some variation in size and shape of the cells. A fragility test was negative. The reticulocyte count was 1.2 per cent, and the white-cell count 13,000, with 80 per cent neutrophils. The urine showed a specific gravity of 1.008, a ++ test for albumin and no sugar. Bence-Jones protein was absent. Several

stools were brown and guaiac negative. The non-protein nitrogen was 25 mg, the protein 6.8 gm and the sugar 107 mg per 100 cc. Gastric analysis showed free hydrochloric acid.

One examiner believed that he felt an irregular mass to the left of the umbilicus and suggested pentoneoscopy. This was done on the tenth hospital day. No masses were visible anywhere in the peritoneal cavity or in the pelvis. The uterus and ovaries were not abnormal. The liver appeared normal and extended three or four fingerbreadths below the costal margin. A liver biopsy was taken during this procedure, and microscopical examination showed no abnormality. The patient was discharged on the eighteenth hospital day.

Final admission (two months later). During the following two months the symptoms continued essentially unchanged. The patient remained on a bland diet, taking iron and vitamins.

X-ray examination showed the stomach to be somewhat dilated, with increased peristalsis. The barium passed readily through the pylorus into the first and second portions of the duodenum, where there was some dilatation. In spite of the increased peristalsis there was a marked delay at this point. There was regurgitation from the duodenum back into the stomach, and only a small quantity of barium passed around the duodenal loop during fluoroscopic examination. Two hours later most of the barium was still in the stomach and duodenum, and only a small quantity had reached the lower jejunum. Six hours after fluoroscopy there was little change. Further examination showed an area of ulceration, 3.5 cm in diameter, in the upper jejunum. The lumen was irregularly dilated. A number of loops appeared to be adherent, and a mass corresponding to the lesion in the bowel was palpated.

Three transfusions were given, and an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR BERNARD M. JACOBSON. This is undoubtedly a case of small-bowel obstruction probably extending over a period of two years. Since I am on the medical service, I am indeed flattered to be presented with such a case. I shall try to uphold the honor of that service in making the diagnosis. I am sure, however, that there are several points about the diagnosis that I shall miss entirely.

The record states that the patient had anemia eighteen months before the first admission. Although she received liver injections for a few months, I believe that the later evidence is sufficient to rule out a liver-deficiency anemia. Certainly, the appearance of the blood is not that of pernicious anemia. The presence of free hydrochloric acid is additional evidence against pernicious anemia, as is the fact

that a course of liver injections gave no improvement.

A yellow color developed and cleared slowly. I have no idea what this was. It may have been due to a common-duct obstruction, which I do not believe has any relation to the present illness. We are reminded on several occasions that she continued to lose weight despite a fair appetite and despite the subsidence of vomiting and pain. One begins to wonder about malabsorption of food or food products due to diffuse small-bowel disease of some sort. We are told that six months before admission, the systolic blood pressure was 86, that the skin was brownish and that some sort of injections and ten salt tablets daily were given. On the basis of these data it is difficult to make a diagnosis of Addison's disease. The record contains no reference to pigmentation of the skin or mucous membranes and no statement regarding chemical investigation of the electrolytes; there is also no later mention of treatment for Addison's disease. The fact that the patient became edematous indicates overdosage of desoxycorticosterone acetate. During the course, no note is made of the passage of a Miller-Abbott tube for diagnostic purposes in conjunction with the x-ray studies. One wonders why that procedure was not done at the time of the first admission, in view of a history suggestive of small-bowel obstruction. Was a Miller-Abbott tube passed?

DR TRACY B. MALLORY. No.

DR JACOBSON. The blood studies indicate a moderately severe hypochromic microcytic anemia. This anemia was the nondescript type that is observed in a large variety of conditions. The normal fragility test and reticulocyte count and the lack of icterus are evidence against the presence of hemolytic anemia, and the normal reticulocyte count is also against the presence of a recent severe intestinal hemorrhage. On the other hand, long-continued oozing of blood can occur in small amounts without a high reticulocyte count as evidence of regeneration in the bone marrow. The figures do not suggest a primary blood dyscrasia, such as leukemia or aplastic anemia. I might add that I do not believe I shall ever be able to explain the anemia properly. I have seen several patients with tumor of the small or large bowel in whom there was no history of frank bleeding, with guaiac-negative stools, and in whom a similar anemia was fairly resistant to treatment. I do not believe that we can rule out occasional slow oozing in this patient, and yet we have no evidence for it. The serum protein of 6.8 gm per 100 cc is rather high for a person with severe anemia, and assuming that she was not dehydrated when the blood was taken, I wonder if we are dealing with one of the several conditions that cause hyperproteinemia. There is certainly no evidence of the most frequent condition that occurs with anemia—namely, myeloma. On the

other hand, it must be remembered that a small proportion of other types of lesions, such as granulomas, do show high serum proteins. It is interesting that peritoneoscopy at the first admission revealed no masses in the abdomen. Peritoneoscopy was informative certainly in that the liver biopsy ruled out amyloid disease, which is one of the conditions that the record suggests.

May we see the x-ray films taken at the time of the final admission?

DR STANLEY M. WYMAN: The first film was taken at the first admission and shows a normal-appearing stomach, duodenal cap and duodenal loop. No abnormal masses can be seen. A review of the films of the first admission suggests some irregularity in the region of the small intestine. The film taken during the second admission shows the irregularity described somewhat better, and it appears to be a filling defect of the lumen of the small intestine. The exact contour cannot be well outlined. The mucosal pattern in this region is no longer present.

DR WALTER BAUER: You have no hesitancy in saying that the mucosa is ulcerated?

DR WYMAN: I believe that it is.

DR JACOBSON: Is there anything that looks like pipestem infiltration in the small bowel?

DR WYMAN: A sclerosing process? I do not believe so.

DR JACOBSON: The ulcerating process and the obvious x-ray evidence of obstruction in the upper part of the small intestine compel me to consider the differential diagnosis of obstruction. Inasmuch as we are told that there was an area of ulceration in the mucosa, the differential diagnosis becomes considerably limited. As I look back over the case, the period of two years with similar symptoms makes it seem logical to assume that this was a tumor, either benign or possibly mildly malignant, that started either in the lymphoid patches or the muscularis and gradually became larger, penetrating into the lumen and involving the serosa and extraintestinal tissues. I do not believe that there are many tumors that can present these symptoms over a period of two years. Certainly the location of the palpable mass in the abdomen is consistent with the location of this lesion somewhere in the jejunum. I should like to characterize the behavior of the tumor for two years by calling it a lymphosarcoma that probably showed, at an early stage, some intraluminal protrusion and caused the early symptoms of pain and vomiting and obstruction, possibly through the mechanism of repeated intussusception. It is only later in the patient's course that we have evidence that the tumor began to ulcerate. I believe that this tumor had grown outward, adhering to many coils of the small intestine, and had finally begun to present a mass that could be felt. I suspect that the lesion was much more extensive in the small bowel than the x-ray evidence indicated. The

extensiveness of the tumor was due to the early presence of malnutrition, possible malabsorption of certain food stuffs and the early presence of a severe refractory anemia. Possibly, the serum protein of 6.8 gm was caused by a lymphosarcoma, which occurs in some cases, but I do not want to stress the importance of any one laboratory finding of that sort. There were undoubtedly metastases to the mesenteric lymph nodes. I am not completely satisfied with the explanation of the anemia or of the hypotension, the yellow color eighteen months previously and the more recent history of a brownish color. My diagnosis is lymphosarcoma of the jejunum with regional intestinal involvement and ulceration of the mucosa.

A PHYSICIAN: How about the pancreas?

DR JACOBSON: In view of the ulceration of the mucous membrane of the jejunum on x-ray examination it seems to me that the tumor probably arose from the small intestine rather than from extraintestinal structures.

CLINICAL DIAGNOSIS

Carcinoma of jejunum

DR JACOBSON'S DIAGNOSIS

Lymphosarcoma of jejunum

ANATOMICAL DIAGNOSIS

Adenocarcinoma of jejunum

PATHOLOGICAL DISCUSSION

DR MALLORY: This patient was operated on by Dr Sweet. I am sorry that he is not here to describe his findings at first hand. A large tumor of the jejunum was found within 10 cm of the ligament of Treitz. The tumor involved the wall of the bowel and the adjacent mesentery and had seeded itself on another loop of jejunum, which had become adherent to it. At operation it had evidently been extremely difficult to preserve the blood supply of the transverse colon, but it was possible to resect the two loops of intestine and the large mass in the mesentery.

The specimen in the laboratory was an ulcerated tumor of the jejunum on the mesenteric side that did not completely encircle the bowel. The major mass of tumor lay in the mesentery and was 6 to 7 cm in diameter. On microscopical examination it turned out to be a well differentiated, slowly growing adenocarcinoma of the jejunum. Cancers of the small bowel are relatively rare, but they do occur from time to time.

DR JACOBSON: How much of the jejunum was actually involved?

DR MALLORY: A small amount of jejunum was directly involved by the tumor, but the links and the adhesions may have thrown a considerable portion more or less out of function.

CASE 33202

PRESENTATION OF CASE

A seventy-eight-year-old widow entered the hospital from a home for the aged complaining of severe abdominal pain and vomiting.

She had been well until three days previously, when, after a normal meal, she began to have intense, cramping abdominal pain in the midepigastrium with vomiting. Following this attack she continued to have intermittent sharp cramping pains radiating across the midabdomen every two to five minutes. Occasionally, the pain was referred to the back but never to the shoulder or the interscapular region. She could take nothing by mouth without vomiting, the vomitus often consisting of greenish, foul-smelling material. There had been no bowel movements or passage of gas during the five days before admission. Two enemas as well as a laxative, had been given without result. The patient's general health had been good until the abrupt onset of the illness. She had lost no weight, and the bowels had moved regularly without evidence of blood or tarry stools. Two months previously a similar episode of vomiting had lasted only a few hours and had been relieved by bicarbonate of soda.

The past history revealed that both femoral necks had been fractured in falls — the right eight years, and the left eight months previously. Both fractures had been successfully treated by nailing. There had been no abdominal operations or pregnancies.

Physical examination revealed a slightly obese woman in no acute distress. The skin was moderately dehydrated without evidence of cyanosis or jaundice. The lungs were clear. The heart was somewhat enlarged on percussion. No murmurs were heard. The abdomen was diffusely tender without spasm, distention or palpable masses. The liver and spleen were not palpable. Pelvic examination was negative.

The temperature was 99.5°F, the pulse 80, and the respirations 30. The blood pressure was 130 systolic, 90 diastolic.

A plain film of the abdomen showed several gas-filled and fluid-filled loops of what appeared to be small bowel. No gas was seen in the colon. X-ray films of the chest were normal.

Examination of the blood revealed a hemoglobin of 16.5 gm and a white-cell count of 12,500, with 60 per cent neutrophils. The urine showed a specific gravity of 1.012, a +++ test for albumin and no sugar or bile. The nonprotein nitrogen was 28 mg, the protein 8.0 gm, and the fasting blood sugar 149 mg per 100 cc, and the chloride was 98 milliequiv per liter. The serum amylase was 14 units. The van den Bergh reaction was 0.7 mg per 100 cc direct and 1.0 mg indirect.

A Miller-Abbott tube was introduced, and intravenous fluids with dextrose and Amigen were ad-

ministered daily. The patient continued to have occasional bouts of cramping abdominal pain. On the third hospital day a prophylactic bilateral femoral-vein interruption was done. The progress of the Miller-Abbott tube was followed by daily x-ray study. The tube progressed slowly through the proximal small bowel, several loops of dilated small bowel being noted distal to the advancing tip. By the seventh hospital day the tube had reached the distal ileum. At that time a single loop of dilated small bowel was seen on the left in the mid-abdomen. A barium enema done on this day showed a good flow, without hesitation, to the cecum through a spastic colon. Numerous diverticula were noted throughout the colon. The terminal ileum was not seen. Several linear shadows were found in the right upper quadrant and were thought to outline the biliary tree. An overexposed film taken to clarify the situation in this area showed gas outlining the stomach and the duodenal cap. Overlying the latter shadow were several irregular linear collections of opaque material whose location was uncertain but was thought to be in the biliary tree. There appeared to be gas in a thin, branching channel extending upward from the location of the duodenal cap.

During the second week of hospitalization there were periods of freedom from pain. The patient passed several stools, consisting mostly of barium, and occasionally passed some gas. She remained essentially unchanged, however, with recurring pain, slight distention and some hyperactive peristalsis.

On the nineteenth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR EDWARD HAMLIN, JR. May we see the x-ray films?

DR STANLEY M. WYMAN. The chest films are essentially those of a woman with a moderately large heart, there is nothing specific about the picture. This next film shows the dilated small intestine and the Miller-Abbott tube starting down through the stomach. In a later examination a branching pattern of what seem to be gas-filled tubes is outlined in the right upper quadrant overlying the shadow of the liver. At the same time linear collections of increased density, apparently barium, lie in the region of the duodenal cap. These are the diverticula in the colon.

DR HAMLIN. Was barium given by mouth at any time?

DR WYMAN. I believe that she was given one small swallow of barium.

DR HAMLIN. That is important because otherwise it would be difficult to determine how barium reached the small bowel.

Can you demonstrate the air-filled biliary tree?

DR WYMAN I think that it is best seen in this film. This looks like the common duct, with shadows representing branching hepatic radicles.

DR HAMLIN The problem is one of an elderly person who obviously had small-bowel obstruction, probably not entirely complete. I say that because at entry, after difficulty for five days, there was relatively less evidence of small-bowel dilatation than she had later when she was being treated more adequately. In the later stage gas passed through when the Miller-Abbott tube was down, so that obstruction was not complete all the time.

The causes of small-bowel obstruction are many. The fact that there had been no previous operations is important. The patient was slightly old to have had congenital bands or adhesions, although I suppose that either diagnosis is a possibility. There is nothing in the x-ray picture to lead one to believe that she had volvulus of any sort, nor does the history suggest it. The lead that is given in the protocol, concerning the outline of the biliary radicles, cannot be ignored for obvious reasons, and immediately one thinks of gallstone ileus. I am going to believe that she had that without any question.

It is of interest to discuss an elderly person with dehydration and the treatment of obstruction. Several years ago Dr McKittick and I effectively demonstrated that in a patient with intestinal obstruction who is seen within the first twenty-four hours and in whom operation is done at once, the mortality rate will approach zero. If the patient is seen after the first twenty-four hours the hazard of anoxemia of a section of bowel is probably less than that of operation with the dilated loops of bowel that would be present. The treatment of this patient followed Dr McKittick's teaching in that she was hydrated, a Miller-Abbott tube was passed and kept down until the bowel was considerably less dilated, and the operation presumably was a fairly easy one and far less hazardous for her than if it had been done in the earlier period. To carry out this type of preoperative treatment is extremely important. Why it required nineteen days, I do not know. I think that the service deserves considerable credit for keeping her in an electrolytic and fluid balance for that period.

Gallstone ileus is a relatively rare condition, consisting of a large gallstone that produces inflammatory adhesions between the gall bladder and the small bowel. Gradually the gallstone passes into the lumen of the small intestine. Because of the large size of the stone, it is almost invariably found at the terminal ileum. The obstruction is almost always complete.

CLINICAL DIAGNOSIS

Gallstone ileus?

Band adhesion obstruction secondary to old diverticulitis?

DR HAMLIN'S DIAGNOSIS

Gallstone ileus

ANATOMICAL DIAGNOSIS

Gallstone ileus

PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY Dr Risley, will you describe the operative findings?

DR THOMAS S RISLEY As Dr Hamlin prophesied, at operation a gallstone was found, but not at the ileocecal valve. It was somewhere in the midileum. There was no necrosis of the bowel at the site of the stone, and there was no obvious reason why the stone should have stopped at that particular point. The stone was movable, and it was relatively simple to milk it upward to a point above, where the bowel was more normal in appearance. It was pushed back several feet above the point where the bowel was edematous and dilated and palpable. There were numerous adhesions in the upper quadrant, but no stones were

DR MALLORY The region was not explored.

DR LAURENCE L ROBBINS, have you ever been able to demonstrate stones in the small bowel? have, but of course certainly. Occasionally, we find little calcium that such a demonstration is often impossible. I believe that in this case the stone following removal showed a few flecks of calcium, but we were never able to identify a film of the ordinary films.

DR MALLORY A gallstone that produces obstruction in the small bowel must be large, and gallstones consist chiefly of cholesterol and contain little calcium. One would not expect a high percentage of them to show roentgenologically.

As Dr Hamlin pointed out, this kind of stone is too large to go through biliary passages of normal size. The chances are at least nine out of ten that there is a fistula between the gall bladder and the intestinal tract through which the stone passed. That was not demonstrated in this case because the patient was old and had had intestinal obstruction for a long period, so that extensive exploration was probably not considered to be justified.

DR BENJAMIN CASTLEMAN How often have you seen gallstone ileus with carcinoma?

DR. MALLORY I do not remember having seen it

DR. BERNARD M. JACOBSON How large does the stone have to be?

DR. MALLORY This one was 3 cm in diameter

DR. WALTER BAUER We had one a few years ago that was found during a gastrointestinal series — a barium-filled, instead of an air-filled, biliary tract

DR. FLETCHER H. COLBY The delay of nineteen days is interesting. Why was operation delayed?

DR. RISLEY The obstruction was quite incomplete, and it appeared at one time as if the obstruction would be spontaneously relieved. It was thought that if the patient had a gallstone she might pass it. She was in poor condition, and it was hoped that the exploration might not be necessary. She was given a trial with removal of the Miller-Abbott tube and had a normal bowel movement, and it

looked briefly as if the obstruction had been relieved; shortly after removal of the tube, however, she became obstructed once more. The first obstruction required quite a time for sufficient decompression to make exploration easy, and the same situation was encountered with the second obstruction.

DR. MALLORY It is of interest that a patient can have such severe disease of the biliary tract as this patient must have had with nothing in the past history to suggest such a condition. She had been in the hospital on two or three previous occasions, and at no time did she complain of symptoms referable to the biliary tract.

DR. BAUER Is that unusual? The incidence of gallstones at autopsy is high, is it not?

DR. MALLORY Yes, but not in association with ulcerative cholecystitis.

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

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SUBSCRIPTION TERMS \$6.00 per year in advance, postage paid, for the United States (medical students, \$3.50 per year) Canada, \$7.00 per year (Boston funds) \$8.50 per year for all foreign countries belonging to the Postal Union

MATERIAL should be received not later than noon on Thursday, three weeks before date of publication

THE JOURNAL does not hold itself responsible for statements made by any contributor

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15 Massachusetts

STREPTOMYCIN

STREPTOMYCIN has been generally available to the medical profession of this country for several months, and by now, most physicians, particularly those who are privileged to treat or to follow the course of patients in hospitals, have had the opportunity of observing the use of streptomycin in occasional patients of their own or of their colleagues. A considerable literature dealing with this antibiotic has also accumulated, and many clinical reports have become available, particularly during the past year. Many additional reports of its use will undoubtedly continue to appear in the near future. A fairly thorough review of the available literature on this topic is presented in this issue and in the preceding issue of the *Journal*.

Streptomycin, as pointed out in this review, has not lived up to all that was expected of it when it first made its appearance. Perhaps the profession had been led to expect too much because of the brilliant results that had so recently been achieved with penicillin. It has, however, proved quite useful, and without doubt, many persons already owe their recovery from various serious infections to treatment with streptomycin. It has provided an effective cure for certain infections for which other available antibacterial agents have not proved successful and offers an alternative or additional agent in some infections that are only partially affected by sulfonamides, penicillin or specific immune serums. It is the first agent to receive careful and extensive study in the treatment of tuberculosis, with some promise of at least limited success.

The exact place that streptomycin will occupy in the treatment of infections, particularly tuberculosis, cannot be predicted at this time. Its greatest disadvantage has proved to be the great ease with which resistant strains become established during the course of treatment. This alone may eventually limit, if not entirely vitiate, its usefulness in tuberculosis and in other infections, particularly those whose courses tend to be subacute or chronic. Its toxicity, although not of a high order, is significant. This is particularly true of the otic complications, which seem to be caused by the antibiotic itself and not by any impurity and which may leave serious and possibly permanent damage. Moreover, the treatment is expensive by any standard, and is likely to remain so. This is bound to be an important deterrent to its widespread use, particularly in view of its other limitations.

These facts justify a sustained and intensive effort to discover new, more potent and more widely effective chemotherapeutic and antibiotic agents. The discovery of the chemical structures of penicillin and streptomycin and the recent advances in the knowledge of bacterial metabolism in relation to chemotherapy offer considerable hope for synthesis of such agents in the not too distant future. In the meantime, the best use should be made of the agents that are now available.

FULL UTILIZATION OF HOSPITAL FACILITIES

A LETTER dealing with certain aspects of hospitalization appears elsewhere in this issue of the *Journal*. The correspondent's points are well taken, and from a businessman's point of view, it certainly is a waste of time and of invested capital to have facilities such as the operating room and the x-ray and laboratory departments functioning only part time. That this results in a great waste of bed days so far as the total number of patients is concerned is unquestionable. On the other hand, if beds are filled

at all times, it seems reasonable to assume that the revenue to most financially embarrassed hospitals would not be appreciably greater whether the occupant of the individual bed changed every seven days or every fourteen. Fees for specific services would increase, but this would probably be counterbalanced by the cost of the necessary additional personnel. There would, however, be a decrease in the unit overhead cost, which in institutions such as the large teaching hospitals might result in considerable saving.

Regardless of the financial considerations, in these difficult days it is essential that hospital facilities should be used for the greatest good for the greatest number, indeed, about a year ago the need of a "seven-day week" was commented on editorially in the *Journal**. The fact is inescapable that if a patient is occupying a hospital bed unnecessarily long it is a waste, and it is suggested that all hospitals, whether privately endowed or financed by community, state or nation, should seriously consider a change from a method of operation that results in such an obvious loss of urgently needed facilities.

*Editorial. Inadequacies of medical care. IV. Those concerning the hospital. *Am. J. Med.* 234:613, 1946.

MASSACHUSETTS MEDICAL SOCIETY DEATHS

BOYLE — John F. Boyle, M.D., of Lowell, died April 25. He was in his seventy-sixth year.
Dr. Boyle received his degree from Harvard Medical School in 1903. He was a former president of the Middlesex North District Medical Society and was a member of the New England Obstetrical and Gynecological Society.
A sister survives.

CARSLEY — Sidney R. Carsley, M.D., of Palmer, died April 19. He was in his seventy-second year.

Dr. Carsley received his degree from University of Vermont College of Medicine in 1902. He was medical examiner for the Eastern Hampden District and was a member of the staffs of the Mary Lane Hospital, Ware, and the Springfield Hospital. He was a fellow of the American Medical Association.

His widow and a son survive.

CASWELL — Bertram H. Caswell, M.D., of Somerville, died April 14. He was in his seventy-second year.

Dr. Caswell received his degree from Tufts College Medical School in 1903. During World War I he served as a captain in the Army Medical Corps. He was a member of the New England Otological and Laryngological Society and a fellow of the American Medical Association.

His widow and a step-daughter survive.

HUNT — William O. Hunt, M.D., of North Falmouth, died April 19. He was in his ninety-third year.

Dr. Hunt received his degree from Harvard Medical School in 1877. He was the last surviving founder of Newton Hospital. Until his retirement from active practice in 1940, he had practiced medicine in Newtonville for fifty-nine years.

A daughter, four sons (one of whom, Dr. Harold O. Hunt, is a resident of North Falmouth), thirteen grandchildren and five great-grandchildren survive.

RONEY — Hugh B. Roney, M.D., of Pittsfield, died January 8. He was in his sixty-first year.

Dr. Roney received his degree from Hahnemann Medical College and Hospital of Philadelphia in 1909. He was a member of the staffs of the House of Mercy and Hillcrest hospitals, Pittsfield.

MISCELLANY

NEW MEDICAL DEAN AT BOSTON UNIVERSITY

Dr. James M. Faulkner, director of the First and Third Medical Services, Boston City Hospital, and professor of medicine at the Tufts College Medical School, has been appointed dean of Boston University School of Medicine. Dr. Faulkner will succeed Dr. Donald G. Anderson, who has resigned as of June 1, to accept a position as secretary of the Council on Medical Education and Hospitals of the American Medical Association in Chicago.

Dr. Faulkner, the son of the late Dr. Herbert K. Faulkner, of Keene, New Hampshire, graduated from Harvard College and Harvard Medical School, and received training at the Massachusetts General Hospital, Rockefeller Institute for Medical Research and Johns Hopkins Hospital. He was associated with the Harvard Medical School at Thorndike Memorial Laboratory of the Boston City Hospital for ten years, being in charge of the Electrocardiographic Laboratory. He later joined the staff of the Boston University School of Medicine and the Massachusetts Memorial Hospitals, where he was in charge of the cardiac clinics.

Dr. Faulkner served in the Navy during the war, being in charge of the medical service at an English base hospital that cared for patients evacuated from the Normandy beach head. He received a commendation from Admiral Stark for this work, and attained the rank of captain before his discharge.

PASSANO FOUNDATION AWARD

Selection of Dr. Selman A. Waksman, microbiologist at the New Jersey Agricultural Experiment Station, New Brunswick, New Jersey, as the 1947 recipient of the Passano Foundation Award has recently been announced by the Board of Directors of the Foundation. Established in 1943 by Williams & Wilkins Company, medical publishers, of Balti-

more, the Foundation proposes to encourage medical research, especially that which has clinical application, and has established the award as one of its activities. Dr Waksman receives the award for his original research in the field of antibiotics culminating with his discovery of streptomycin, which among its many uses gives promise of being of value in the successful treatment of tuberculosis.

Presentation of the \$5000 cash award will be made at a dinner to be attended by about a hundred outstanding medical men at the Ritz-Carlton Hotel, Atlantic City, on Thursday evening, June 12, during the week of the centennial meeting of the American Medical Association. Sir Howard Florey, of Oxford, England, who was knighted for his development of the clinical applications of penicillin, will make a brief address, following which the award will be presented to Dr Waksman. Dr Waksman's address will be entitled "Antibiotics and Tuberculosis — a Microbiological Approach."

NOTE

Dr Robert P Knight, at present chief-of-staff of the Menninger Clinic, Topeka, Kansas, has recently been appointed medical director of the Austen Riggs Foundation, Stockbridge, Massachusetts. Dr Edgerton McC Howard, who is now serving as acting medical director, will become associate medical director. Dr Knight will assume his new duties on September 1.

CORRESPONDENCE

"THE LOST WEEK-END"

To the Editor Hospitals today are badly overcrowded and have long waiting lists. Emergency surgical patients are readily admitted in most instances, a spare room or bed is usually reserved for just such a contingency or a temporary arrangement is made, such as placing the patient, even though of private status, in a ward. A medical emergency fares less satisfactorily, and patients who present no emergency but who are ailing and require the facilities of a hospital for diagnosis are placed on the waiting list and have a poor chance of being admitted for weeks or months.

The chief reasons for crowded hospitals appear to be the following: (1) The Blue Cross, the Blue Shield and other types of hospital and medical insurance, which permit benefit if the patient is hospitalized, (2) the widespread use of penicillin, which, to be given effectively, usually requires hospitalization, (3) the scarcity of trained nurses for home duty, (4) the shortage in the hospitals of nursing personnel and technicians, (5) the increased cost of operating hospitals in such a way that they function properly, and (6) the common custom of hospitals to run at low speed during week ends and holidays. The last reason is, in my opinion, an extremely important one. At such times the nursing and technical departments are manned by skeleton crews, which attempt to function only on an emergency basis. Out-patient departments are closed, although there is no doubt that if they were open not only would many be helped who would otherwise hesitate to seek help because of the fear of losing a day's work and pay but also advice would be given to others that might later forestall serious illness for which hospitalization and abstinence from work would become imperative.

As a direct result of the above factors patients are obliged to remain in the hospital, often at great expense to themselves or to industry, to wait their turn for the various special examinations ordered by the physician. A patient who enters the hospital Friday afternoon and who pays \$7 a day on the ward or \$10 or more a day for a private room, does not relish the knowledge that only emergency work will be done for him until Monday and that even some of the work that has to be done may not be reported till Tuesday.

Faced with this unprecedented demand for admissions, what steps have the hospitals taken? They have appealed for more nurses to keep their wards open, and they have raised salaries. It seems to me the one step not taken to increase their usefulness is to eliminate the week-end or holiday vacation. Were this latter step taken, an extra one and a half days would become available weekly for routine hospital diagnostic procedures. Thus approximately a week would be

gained monthly, or seventy-five days yearly, which, added to about eight days for holidays, would amount to nearly three months each year. In this manner, the capacity of the hospital, in so far as routine diagnostic procedures are concerned, would be increased by about a third.

How can the hospital provide for the full-time use of facilities? Obviously, it will be necessary to increase the personnel and to stagger the working hours. A further raise in salaries may be required. To provide for additional medical personnel, it might be possible to arrange for so-called "floaters." Thus, a private roentgenologist might be induced to "spell" his resident brother for a week end or for a specific number of hours each week. The same would be true of the pathologist, anesthetist and so forth. This problem would not differ materially from that of arranging for the summer vacation or for prolonged illness.

The money necessary to run the hospital on this full time schedule would become available from the increased income obtained by the more rapid turnover of patients. In addition, as the improved facilities and service offered by the hospital impressed the community, there would be a greater eagerness to contribute to its support.

ALLEN W LOCKE, M.D.

76 Washington Street
Wellesley Hills, Massachusetts

PROFESSIONAL RESPONSIBILITY

To the Editor In reference to Dr Stratton's statement in the March 20 issue of the *Journal* regarding my recent experience with the Court, I wish to present to the fellows of the Massachusetts Medical Society the facts of the case.

On the morning of February 16, at about 2:00 a.m., I was called to see a young woman who had been criminally attacked. The car in which she and her escort were riding had been stopped by blocking the road, the door window smashed, her escort ordered out by two masked men at gun point, the girl taken out by a third man at gun point and then criminally attacked by the three men in turn.

I was fully satisfied that the girl's story was true, and examination showed unmistakable evidence of assault. Her family made it plain that they wished nothing said of the matter and refused to consult the police. I agreed that it was a private matter and that, so far as I was concerned, their wishes would be respected.

On my return home, however, and on reflection of the incident, I decided that, for the protection of the public, the police should be notified of the affair. That same morning I gave all the details, excepting names, to the police and informed them that I was doing this without the patient's knowledge and against the expressed wish of her family.

Two weeks later, a young man was killed when two gunmen ordered him and his girl companion into the back seat of his car and took possession of the machine. The police then asked me for the identity of the young lady whom I had treated, on the supposition that this murder might have been committed by the same men who had assaulted her.

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These cases are in marked contrast to a patient whom I treated before the sulfonamides were known. In this case the eruption extended in the course of a few days from the spinal cord to the sternum, covering the right, lower thoracic region. It was a solid bright red mass of papules and vesicles, about 7.5 cm. in width. The discomfort and pain were severe, requiring repeated doses of codeine and aspirin to control it. The patient was confined to her bed for nearly a month, with an elevation of temperature for the first two weeks. For six months after the rash subsided she complained bitterly of sharp, shooting pains in the right thoracic region, and even a year after the onset she still had occasional pain.

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Most textbooks state that herpes zoster treated by orthodox methods ordinarily lasts from two to three weeks. My experience, prior to the use of sulfadiazine, leads me to believe that that prognosis is entirely too optimistic. The rash may last or disappear in two or three weeks, but the pain, which is the chief factor, may persist for weeks, months and even years. In my experience herpes zoster treated by orthodox methods is a prolonged, painful malady with an extremely uncertain prognosis.

NEIL C STEVENS

Walpole New Hampshire

AN IMPROVED GASTROSCOPE

To the Editor In spite of the well established usefulness of gastroscopy with the flexible gastroscope, there are still blind areas in the stomach that are relatively inaccessible. These have been partly overcome by the development in England of the Hermon Taylor flexible gastroscope, on the handle of which there is a racket that permits movement of the flexible portion after introduction into the stomach. This permits a much better view of the lesser curvature and anterior wall in the upper part of the body of the stomach. It also enables some increased visibility in the antrum. The slightly larger caliber of this instrument, making it a little more difficult to pass, is far outweighed by the better view obtained. In an occasional difficult case, one may have to revert to the original more flexible type of gastroscope.

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EDWARD B BENEDICT, M D

Massachusetts General Hospital
Boston 14

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The chief reasons for crowded hospitals appear to be the following: (1) The Blue Cross, the Blue Shield and other types of hospital and medical insurance, which permit benefits if the patient is hospitalized, (2) the widespread use of penicillin, which, to be given effectively, usually requires hospitalization, (3) the scarcity of trained nurses for home duty, (4) the shortage in the hospitals of nursing personnel and technicians, (5) the increased cost of operating hospitals in such a way that they function properly, and (6) the common custom of hospitals to run at low speed during week ends and holidays. The last reason is, in my opinion, an extremely important one. At such times the nursing and technical departments are manned by skeleton crews, which attempt to function only on an emergency basis. Out-patient departments are closed, although there is no doubt that if they were open not only would many be helped who would otherwise hesitate to seek help because of the fear of losing a day's work and pay but also advice would be given to others that might later forestall serious illness for which hospitalization and abstinence from work would become imperative.

As a direct result of the above factors patients are obliged to remain in the hospital, often at great expense to themselves or to industry, to wait their turn for the various special examinations ordered by the physician. A patient who enters the hospital Friday afternoon and who pays \$7 a day on the ward or \$10 or more a day for a private room, does not relish the knowledge that only emergency work will be done for him until Monday and that even some of the work that has to be done may not be reported till Tuesday.

Faced with this unprecedented demand for admissions, what steps have the hospitals taken? They have appealed for more nurses to keep their wards open, and they have raised salaries. It seems to me the one step not taken to increase their usefulness is to eliminate the week-end or holiday vacation. Were this latter step taken, an extra one and a half days would become available weekly for routine hospital diagnostic procedures. Thus approximately a week would be

gained monthly, or seventy-five days yearly, which, added to about eight days for holidays, would amount to nearly three months each year. In this manner, the capacity of the hospital, in so far as routine diagnostic procedures are concerned, would be increased by about a third.

How can the hospital provide for the full-time use of facilities? Obviously, it will be necessary to increase the personnel and to stagger the working hours. A further raise in salaries may be required. To provide for additional medical personnel, it might be possible to arrange for so-called "floaters." Thus, a private roentgenologist might be induced to "spell" his resident brother for a week end or for a specific number of hours each week. The same would be true of the pathologist, anesthetist and so forth. This problem would not differ materially from that of arranging for the summer vacation or for prolonged illness.

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CHARLES L. BRENNAN, MD

24 Merrimack Street
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the parent and the school. In the long chapter entitled "In Search of Knowledge" various types of questions propounded by children are noted, and a pattern for answers is suggested by the author. The final chapter discusses the opposition to sex education and the need for such education. In the appendixes will be found a tentative scheme for education, specimen circulars to be sent to parents and specimen lectures on the subject. For reference purposes the absence of an index is to be deplored. This text should prove useful to all interested persons.

Medical Uses of Soap. A symposium. Edited by Morris Fubben, M.D. 8°, cloth, 195 pp. Philadelphia: J. B. Lippincott Company, 1946. \$3.00.

This second printing of a valuable monograph first published in 1945 has an additional chapter on the surgical uses of soap.

Endocrine Function of the Hypophysis. By Harry B. Friedgood, M.D., assistant clinical professor of medicine, University of Southern California School of Medicine, and senior attending physician, Los Angeles County Hospital. 8°, cloth, 211 pp., with 36 illustrations. New York: Oxford University Press, 1946. \$4.50. Reprinted from *Oxford Loose-Leaf Medicine*.

By reprinting this monograph the Oxford University Press makes it possible for interested physicians and small libraries to own this concise but comprehensive treatise without having to procure the complete *Oxford Medicine*. The work is divided into five parts. The first discusses anatomy, embryology and phylogeny of the hypophysis; the second, the cytophysiology and biochemistry of the adenohypophysis; the third, the biologic, biochemical, physiologic and genetic concepts of growth; the fourth, the chemical disorders of growth; and the fifth, the cytophysiology, biochemistry and pharmacology of the neurohypophysis. This monograph should be in all medical libraries and in the collections of all persons interested in the subject.

Principles of Hematology, with 106 Illustrative Cases. By Russell L. Haden, M.D., chief, Medical Division, Cleveland Clinic. Third edition, revised. 8°, cloth, 366 pp., with 173 original photomicrographs and 95 original charts and drawings. Philadelphia: Lea and Febiger, 1946. \$5.00.

This manual is written for the student and physician and not for the specialist, and emphasis is therefore placed on the fundamental principles of hematology. Highly technical procedures, such as the study of the Rh factor, are omitted. The type has been completely reset, and corrections have been made to bring the subject up to date, including a description of the technique of bone-marrow puncture and the study of bone marrow films. The book is well printed on good paper in a good type and is well illustrated.

Life House Physician. By Vice-Admiral Ross T. McInture, Surgeon General of the Navy. 8°, cloth, 244 pp., New York: Putnam's Sons, 1946.

Dr. McInture was the personal physician of President Roosevelt from the day of his first inauguration in 1933 until his death on April 12, 1945, and was also his companion, friend and confidant. He accompanied the President on his many journeys—to Newfoundland, where the Atlantic barrier was signed off the coast, Casablanca, Teheran, and Egypt.

He speaks with authority on the health and physical fitness of the President and of his struggle to overcome his infirmity due to infantile paralysis. He tells of the reasons behind his running for the presidency in 1940 and 1944. The volume is also an inside story of the political life of the presidential years. The text is written in an easy narrative style.

Courage and Devotion beyond the Call of Duty. Being a partial record of official citations to medical officers in the United States Armed Forces during World War II. Second preliminary edition, July, 1946. 12°, paper, 1024 pp. Evansville, Indiana: The Johnson and Company, 1946. Free.

The first issue (November, 1944) contained only 256 pages. The present text is divided into two parts, citations to in-

dividuals and citations to groups. Information is incomplete on a number of physicians and a few groups listed at the end of the volume, and the publisher invites corrections and additions and further information prior to issuing the final deluxe edition. This book is a valuable biographical reference source.

Manual of Applied Nutrition. A publication of the Dietary Department, Johns Hopkins Hospital. Second edition. 8°, paper, 103 pp. Baltimore: Johns Hopkins Hospital, 1946. \$1.50.

This manual has been revised and edited by a group representing several clinical departments and the Nutrition Committee of the Johns Hopkins Hospital. All available knowledge and experience have been used in its preparation, and although compiled for the use of a particular hospital, it should prove useful to clinicians and dietitians everywhere. It contains a wealth of material on all types of diets, general and special, given in terms of food constituents, as well as routines for special hospital services. There is a section on the feeding of infants and children. Other special material includes recommended normal dietary allowances for men, women and children, tables of normal measurements of males and females from birth to twenty years in relation to age and height, physiologic data concerning biologic body substances, food values of common substances, data for acid-base calculations, routine house diets and high-calorie diets. This text should prove valuable to medical librarians as a reference source.

Health Examinations. Prepared for the Medical Society of the County of New York by the Special Committee on Preventive Medicine. 8°, paper, 144 pp. Reprinted by Mead Johnson and Company, 1946. Free.

In this short manual a number of physicians discuss briefly the various topics relating to health examinations in young and old persons, from the newborn infant to persons over sixty-five years of age. Included are chapters on premarital and prenatal examinations, the emotional development of children from birth to the sixth year and from the sixth to the twelfth year, the psychology of adolescence and the emotional factors in senescence. Emphasis is placed on the healthy adult, especially between forty-five and sixty-five years of age. Special chapters are devoted to the ears, eyes, teeth and nutritional deficiency diseases. These outlines should prove useful to all physicians called on to make periodic health examinations.

A Memoir to the Academy of Sciences at Paris on a New Use of Sulphuric Ether. By W. T. G. Morton, of Boston in the U. S. A. Presented by M. Arago in the autumn of 1847. With a foreword by John F. Fulton, M.D. \$1.50. Historical Library, Yale Medical Library, Publication No. 14. 8°, paper, 24 pp. New York: Henry Schuman, 1946.

In this memoir, written by Morton in his twenty-eighth year, he gives the background of his discovery and the relations of his claims to those of Wells and Jackson. The appendix printed with the original French edition, but not reprinted in *Littell's Living Age*, is omitted in this reprint. The original memoir is rare, and this inexpensive edition should be welcomed by all persons interested in medical history and should be in all medical-history collections.

Notes on Nursing. What it is, and what it is not. By Florence Nightingale (London, 1859). 8°, cloth, 79 pp. Reprinted Philadelphia: J. B. Lippincott Company, 1946. \$1.25.

This reprint is an exact offset facsimile of the original printing of a classic in the field of nursing. It includes even the advertisements appended to the text. It is recommended for all libraries, medical, nursing and public, and this inexpensive edition makes the volume available to all nurses and others interested in the history of nursing.

Psychotherapy in General Medicine. By Geddes Smith, associate, The Commonwealth Fund. 8°, paper, 38 pp. New York: The Commonwealth Fund, 1946. 25 cents.

This pamphlet gives a detailed report of a postgraduate course in psychotherapy conducted in April, 1946, at the Center of Continuation Study, University of Minnesota.

subject has been handled mainly as a series of superimposed changes of architecture. One may say with reasonable certainty that it is now reasonably complete — just as gross morphology was quite definitely established seventy-five or ninety years ago.

For many years Dr. Patten has contributed heavily to the development of this science, and he is admirably suited, both by his knowledge and his genius for exposition, to writing this volume, which stands as an excellent and quite complete codification of the morphology of embryology.

It is well to have available such a well crystallized and understandable text of this aspect of embryology, for one may dare to assert that we stand on the threshold of a more comprehensive science of the embryo — a science in which successful attempts have already been made in physiology, chemistry and pathology.

A few examples may be chosen from divergent fields: the experiments in embryo mechanics, including the potency of isolated anlage and the presence of "organizers" of "energizers" developed in the writings of Spemann, Waddington and Weiss, the influence of the sexual hormones on both sexual and other development — for example, that of estrogen on bone growth (Bremer), the influence of transmitted defects of the glands of internal secretion on body build (Stockard), and the time of assumption of function by the various organs, such as the prenatal and postnatal maturation of the various parts of the nervous system (Conel).

A few problems of embryonic pathology have been explained: the transmission of congenital defects from "tainted" stock, the cause and prevention of erythroblastosis fetalis and the causation of congenital defects by rubella in the mother.

The aim of the comprehensive embryology of the future appears to be to make embryology now and in later times no longer merely a preclinical science but one of daily clinical application. It is necessary for the intelligent physician to familiarize himself with embryology. For him, as well as for the medical student, this work may be heartily recommended. It is authoritative and written lucidly and with much emphasis on application. The format is likewise excellent, with many fine drawings.

Group Psychotherapy: Theory and practice. By J. W. Klapman, M.D. 8°, cloth, 344 pp., with 14 illustrations. New York: Grune and Stratton, 1946. \$4.00.

The expression "so many and so few" may well be applied to the present situation regarding the mentally ill and the number of psychiatrists available. Group psychotherapy arose out of dire necessity and is still in the formative stage. This book is of value not only to sum up past and present knowledge in the field but also to point the way for the formulation of technique.

After a brief account of the development of group psychotherapy, the author traces its mental, moral and cultural origins. The developmental defects due to social isolation are emphasized, and the unique value of the demonstration of social standards and social conscience in group psychotherapy is indicated.

Methods used vary from the analytic school to the repressive, inspirational modes of psychotherapy. The personality of the therapist is of great importance. The action of numerous intragroup factors is described. Whenever possible, the procedure should be used in conjunction with individual psychotherapy.

Group psychotherapy is viewed as a method of affective re-education — "an adjustment of internal relations to external relations." For this purpose the lecture method and class and discussion periods are valuable. The psychodrama is used to "bring the patient to maturity by easy and gradual stages."

Other fields for group psychotherapy are in the outpatient clinic, for the treatment of problem children and their mothers and in private psychiatric practice.

Ancillaries to group psychotherapy are encouragement of hobbies and special interests, clubs, special radio programs, institutional publications and a public-relations program for mental hospitals.

The results are difficult to estimate. By means of a number of objective tests and evaluation by therapist and patient, they appear gratifying. Education by any method is a long-term project.

Oral Medicine. By Lester W. Burket, M.D., D.D.S. With a section "Oral Aspects of Aviation Medicine," by Major Alvin Goldhush, D.C., A.U.S. 8°, cloth, 674 pp., with 350 illustrations. Philadelphia: J. B. Lippincott Company, 1946. \$12.00.

In this volume the objective of correlating many of the diseases of the oral cavity with systemic disease has been successfully reached. The author, who is a physician and dentist studying oral disease in a well organized clinic, is especially fitted to evaluate and stress the diagnosis and treatment of the important and frequent diseases of the oral cavity.

Case records of the patient with oral disease should include a detailed history, with a description of the lesions and all the pertinent laboratory procedures that are used in the diagnosis of any pathologic process in the body. This the author has accomplished by a complete type of record used in the department of oral medicine.

Ten sections, which include all aspects of diseases of the oral cavity, as well as a regional diagnostic index, give a complete coverage of oral disease. Ten color plates with sixty subjects are especially useful in depicting some of the more frequent diseases of the tongue and buccal mucosa.

One criticism of the volume is the tendency to include discussions on many local and systemic diseases that are unrelated to oral disease. Reference to books on general medicine would serve as more practical guides to the dentist or dental student in rounding out his knowledge of the relation of constitutional and oral disease.

The book can be recommended as a textbook in oral medicine for the dental student and as a guide to the practicing dentist and physician in correlating lesions of the oral cavity and disease found elsewhere in the body.

Western Reserve University Centennial History of the School of Medicine. By Frederick C. Waite, A.M., Ph.D. 8°, cloth, 588 pp., with 15 illustrations and frontispiece. Cleveland: Western Reserve University Press, 1946. \$6.00.

This centennial volume records, after the pattern of the Chinese drama, the history of the School of Medicine of Western Reserve University as a series of episodes in a progressive educational institution in which the professors are the chief actors and the students are the audience. In so doing, it epitomizes the history of medical education prior to the foundation of Western Reserve in 1843. An account is also given of the three rival local medical colleges, of homeopathic medical education in Cleveland and of several local hospitals. The work thus becomes a history of all institutional medical education in Cleveland during its first hundred years. The volume is divided into five books — a prologue, "The First Half-Century," "Ancillary Events," "The Second Half-Century" and biographical material constituting an epilogue.

The author, well known as a medical historian for his work on Vermont Medical College, was a teacher at Western Reserve for over fifty years, having been appointed professor of histology and embryology in 1901. His volume, which is exceptionally well written and entertaining, is a valuable and scholarly contribution to the history of medical education in America.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Sex Education: A Guide for parents, teachers and youth leaders. By Cyril Bibby, M.A., M.Sc., F.L.S., education officer to the Central Council for Health Education, England. 8°, cloth, 311 pp. New York: Emerson Books, Incorporated, 1946. \$2.50.

This English book has been revised by the changing of words and phrases having different meanings in the United States and by the deletion of passages not of interest to American readers. Footnotes have been added explaining British conditions. The subject is discussed from the viewpoints of

The New England Journal of Medicine

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Volume 236

MAY 22, 1947

Number 21

THE SHATTUCK LECTURE

THE CLINICAL SIGNIFICANCE OF SOME PECULIARITIES OF THE CIRCULATION IN THE KIDNEYS, LIVER, LUNGS AND HEART*

WILLIAM DOCK, M.D.†

BROOKLYN, NEW YORK

REFLECTION on the functional significance of the valves in the veins and in the heart led Colombo and Cesalpino to postulate a circulatory system in place of the long-accepted tidal flow of blood from the liver and heart. These anatomic peculiarities of the vascular system were also emphasized by Harvey, who first gave a quantitative description of the motion of the blood, based on the structure of the human heart and on experiments on living animals. In the past three decades more progress has been made in the quantitative study of the circulation of the viscera of man and animals than had been achieved in the previous three centuries. Much of this advance has been made possible by new technical methods, but data of some interest have also been obtained by the injection or perfusion of human organs post mortem by means of a technic that was possible even in the days of Harvey, and decisive answers have been given by animal experiments of a relatively crude and simple nature. Both methods were used to obtain quantitative answers to the query, What is the need of this organ for blood and what is the capacity of its vascular bed?

The blood supply of an organ must meet its needs during maximal activity. In muscles, the heart and digestive glands such as the parotid gland and the pancreas the need for oxygen during activity is many times that under basal conditions. A complete description of the circulation of an organ, in health or disease, must include an estimate of the oxygen needs, basal and maximal, the capacity of the vascular bed and the volume flow under varying conditions. The rates of flow during life are of utmost interest, and in the kidneys, liver and

brain they can now be measured with some accuracy in unanesthetized men as well as in animals. The measurement of capacity for post-mortem flow will be most informative if it can be compared with rates of flow measured during life, just as all post-mortem studies in the past have been given significance by correlation with careful clinical observation.

THE KIDNEYS

The kidneys may well be described as the organs that "work while you sleep." Their blood flow and excretory work are maximal under basal conditions and during fever, but drop off during effort, falling to extremely low levels when the body is violently active or under such stresses as are imposed by shock or hemorrhage.^{1,2} One might say that the function and blood flow depend on how much blood can be spared from other tissues. This paradox of behavior was the first and most remarkable discovery made with the modern technics for measuring blood flow in the organs of an intact, unanesthetized animal or those of man.

Most observers agree that renal blood flow and oxygen uptake are not related to excretory activity, but their conclusions are based on experiments that did not evoke a wide range of variations in osmotic work. The rat can secrete urine with a 10 per cent urea content, and the osmotic work is then almost sixty times as great as that of the kidneys of a rat excreting dilute urine with only 0.1 per cent urea.³ The oxygen consumption of the kidneys is augmented only 22 per cent with this enormous increase in osmotic work, but the caloric equivalent of the extra oxygen used is five times as great as that of the extra osmotic work performed (Table 1). In other words, the efficiency with which this extra osmotic work can be handled by the kidneys is 20 per cent—a high level for any vital process. The efficiency of their work when excreting dilute

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 20, 1947.
†From the Department of Medicine, Long Island College of Medicine.
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Twenty-five physicians attended the lectures and seminars for a period of two weeks. The course was given to ascertain whether the general practitioner could be educated at the postgraduate level to care for psychoneurotic patients encountered in his general practice. The immediate results were the recognition by both students and instructors of new possibilities in the general practice of medicine, a warm response by clinic patients to treatment and a conviction on the part of most of the students that their usefulness and morale as physicians had been strengthened.

Sir W Arbuthnot Lane, C.B., M.S., F.R.C.S. His life and work By W E Tanner, M.S., F.R.C.S. 8°, cloth, 192 pp., one portrait. Baltimore: Williams and Wilkins Company, 1946. \$4.50.

This life of an eminent British surgeon covers the whole of his professional career from his student days until he became surgeon to Guy's Hospital. The surgical achievements of a man notable for his work on fractures and abdominal surgery and his advocacy of colectomy are depicted by Mr Tanner throughout the text. One chapter is devoted to a trip to America in 1918 as a member of a committee to stimulate interest in the cause of the Allies. A complete bibliography of Lane's published writings comprising three hundred and forty-six titles, arranged by subjects and compiled by Mr G A R Winston, Will's Librarian of Guy's Hospital, is appended to the text. This biography is recommended for all medical-history collections.

Principles of Neurological Surgery By Loyal Davis, M.D., Ph.D., D.Sc. (hon.), professor of surgery and chairman of the Division of Surgery, Northwestern University School, Chicago. Third edition, thoroughly revised. 8°, cloth, 540 pp., with 192 illustrations. Philadelphia: Lea and Febiger, 1946. \$7.50.

This standard text, intended for the use of medical students and general practitioners, has been revised to include the knowledge gained by the author and others in World War II. The volume is well printed on good paper, and the material is well organized. The illustrations and plates are excellent. The book is recommended for all medical libraries.

Currents in Biochemical Research Edited by David E Green. 8°, cloth, 486 pp. New York: Interscience Publishers, 1946. \$5.00.

This collection of essays covers the whole field of biochemistry and is the joint endeavor of thirty collaborators who are specialists in their particular fields. The work is semipopular in character and written in simple language but on a scientific plane and without sacrifice of scholarship. The contributions emphasize the focal position of biochemical research in biology, chemistry and medicine. They invade the fields of organic, analytical and physical chemistry and encompass pharmacology, chemotherapy, public health, genetics, photosynthesis and agriculture. The contrast between the type used and the soft paper is not good and makes for difficult reading. The volume is recommended for all medical libraries for reference purposes.

Modern Drug Encyclopedia and Therapeutic Index Edited by Alexander B Gutman, Ph.D., M.D., assistant professor of medicine, Columbia University, College of Physicians and Surgeons, attending physician, Presbyterian Hospital, and associate attending physician, Vanderbilt Clinic, New York City. Third edition. 8°, cloth, 1157 pp. New York: York Publishing Company, Incorporated. \$10.00.

This new edition of a standard reference work has been completely rewritten and reset. Obsolete preparations have been deleted, new drugs and biologicals have been added and the arrangement of the material has been simplified. It is planned to keep the volume up to date by the issuance of supplements from time to time in which new preparations will be described. Comprehensive indexes of therapeutic uses and drugs arranged by manufacturers and distributors add greatly to the value of the work. A good general index concludes the volume. The material is well arranged and divided into pharmaceuticals, biologicals and allergens. The text is well printed and the type composition makes for easy use.

The volume is recommended for all medical libraries and should prove valuable to physicians and others.

Clinical Laboratory Diagnosis By Samuel A Levinson, M.D., Ph.D., director of laboratories, Research and Educational Hospitals, Chicago, and professor of pathology, University of Illinois College of Medicine, and Robert P MacFate, Ch.E., M.S., Ph.D., assistant director of laboratories, Research and Educational Hospitals, Chicago, and assistant professor of pathology, University of Illinois College of Medicine. Third edition, thoroughly revised. 8°, cloth, 971 pp., with 192 engravings and 15 plates. Philadelphia: Lea and Febiger, 1946. \$10.00.

This standard treatise has been brought up to date, and a few new methods have been added. The chemical methods have been critically revised, and all other laboratory procedures have been changed to conform to the latest methods. A new chapter on tropical medicine and new material on penicillin in the blood, acid phosphatase, the latest bone-marrow findings with ten new pictures of bone-marrow films, Diodrast and inulin clearance tests, anthocyanin and phenylpyruvic acid in urine have been added. The text is well printed with a good type on heavy paper. The work is recommended for reference purposes.

NOTICES

MASSACHUSETTS PHYSICIANS' ART ASSOCIATION

The first yearly exhibition of works of art by members of the Massachusetts Physicians' Art Association will be held on the fourth floor, Hotel Statler, Boston, throughout the meeting of the Massachusetts Medical Society, May 20 to 22.

MASSACHUSETTS MEDICO-LEGAL SOCIETY

The annual meeting of the Massachusetts Medico-Legal Society will be held in Parlor C, Hotel Statler, Boston, on Wednesday, May 21, at 2.45 p.m.

PROGRAM

The District Attorney and the Medical Examiner. Hon. George E. Thompson, district attorney, Middlesex County.

Business meeting
Refreshments

All medical examiners, whether or not members of the Massachusetts Medico-Legal Society, are cordially invited to attend.

NEW ENGLAND HEART ASSOCIATION

The annual Henry Jackson Lecture, under the auspices of the New England Heart Association, will be given by Professor John McMichael, of the Postgraduate Medical School, London, England, at 8.15 p.m. on Monday, May 26, at the Boston Medical Library. His subject will be "Heart Failure".

A short business meeting will precede the lecture. Interested physicians and medical students are cordially invited to attend.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The general oral and pathology examinations (Part II) for all candidates will be conducted at Pittsburgh, Pennsylvania, by the entire Board from Sunday, June 1, through Saturday, June 7, 1947. The Hotel William Penn in Pittsburgh will be the headquarters for the Board. Formal notice of the exact time of each examination will be sent to candidates several weeks in advance of the examination dates. Hotel reservations may be made by direct application to the Hotel William Penn.

Candidates in Military or Naval Service are requested to keep the Secretary's office informed of any change in address. Applications are now being received for the 1948 examinations. For further information and application blanks address Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh 6, Pennsylvania.

(Notices continued on page xiv)

usually compensatory to renal arteriosclerosis and therefore a "good thing." It is a disturbance of vasomotor tone, probably varying greatly in its origin in different patients, or even in the same patient at different times. What complex interplay exists between the kidneys and the vasomotor center can be dimly perceived and remains to be elucidated.

Studies on the kidneys in shock have cast a new light on the old experiments on renal hypertension. A decrease in blood flow to the kidneys, whether due to a clamp on the renal artery or to shock, leads to a remarkable series of events.⁸⁻¹⁰ The most startling and unique is a decrease in renal metabolism and oxygen use roughly proportional to the decrease in flow of blood in the kidneys. The kidneys not only work while we sleep but also sleep when we are struggling to maintain life. When the renal blood flow is 10 per cent of normal, renal oxygen use is only 10 per cent of normal, and the blood in the renal vein is no more depleted of oxygen than under basal conditions.⁸ When renal blood flow is arrested and later released, the vascular bed of the kidneys is not widely dilated, as it is in a limb or in other viscera after temporary complete ischemia. In the latter sites, the flow instantly rises to many times the basal rate when the artery is released, in the dog it takes nearly an hour for renal vasoconstriction to pass off and for blood flow and metabolism to return to normal after ten minutes of complete arterial block.¹¹

Renal vasoconstriction in dogs and in men occurs after hemorrhage or shock. In man, it takes place in heart failure, or even when an erect posture, with a resulting decrease in cardiac output, is assumed.¹² It also occurs whenever pain, fear or anxiety is suffered.¹ At the times when other tissues require a large part of the cardiac output, the kidneys reduce both their extravagant demand for blood and their use of oxygen. Thus, they accumulate no oxygen debt.

Tigstedt showed that the kidneys contained a heat-labile protein that acted as a vasoconstrictor. More recently, it has been demonstrated that renin is a protein-splitting enzyme, capable both of liberating a pressor amine from one of the globulins of the plasma and of inhibiting the oxygen uptake of isolated slices of renal cortex.¹³ In rabbits, even after repeated injections have exhausted its vasoconstrictor action, renin causes an intense diuresis of fluid with about the composition of plasma filtrate.¹⁴ In a word, it stops tubular reabsorption as effectively as cyanide. Shock apparently leads to the release, in the kidneys, of an inhibitor of renal metabolism that also causes renal vasoconstriction and may cause vasoconstriction generally.

It is worth emphasizing that anoxia has no such effect on the kidneys. When arterial oxygen saturation is low, the uptake of oxygen by the kidneys is normal and renal venous blood is profoundly un-

saturated, renal blood flow increases slightly.⁸ No hypertension follows arterial anoxia. The mechanism for reducing renal metabolism and causing vasoconstriction in the kidneys is set in play only by lowering of the renal arterial pressure or pulse pressure, or by raising of the interstitial pressure in the kidneys. Obviously, such a mechanism can be set off only by acting on a sensitive structure in the vascular bed of the kidneys.

An anatomic structure that might serve such a purpose had been noted in many mammalian kidneys by the histologists, just as the valves of the heart and veins were seen by many anatomists long before Colombo, Cesalpino and Harvey were aware of their functional significance. In this case it was Goormaghtigh,¹⁵ of Belgium, who suggested, in 1939, that the renal pressor mechanism was probably related to the peculiar cells in the afferent arteriole of each glomerulus and the plaque of closely crowded epithelial cells in the distal convolution at the point where it touched the glomerular hilus. This structure takes different forms in various species. It shows unusual cytoplasmic granules, mitotic figures and even hypertrophy in animals subjected to acute renal ischemia.¹⁻¹⁶ Changes in the juxtaglomerular tissue have also been noted after renal trauma and even after shock due to adrenalectomy.¹⁷ In 1943 hyperplasia of this tissue was noted in kidneys of men who had been in shock for several days before death,¹⁸ and photomicrographs were made of such changes in the material at the Army Medical Museum (Figs 1 and 2). Goormaghtigh¹⁹ reported this change in similar material seen in Europe. No such changes are seen in chronic renal hypertension of dogs or rabbits, or in human hypertension of long standing.

Renin may be detected in the blood in some cases of shock and of acute hypertension, but it is not found even in the renal venous blood in chronic hypertension.²⁰ This makes it probable that this renal mechanism was evolved in relation to shock and hemorrhage, which are common hazards of all mammals under natural conditions, but was revealed in the laboratory by throttling of the renal artery — a phenomenon that has no natural analogy in the pathology of rabbits and dogs. The pressor mechanism is perhaps less important than the inhibition of renal metabolism. This protects the kidneys even from many hours of ischemia, whereas muscles and other structures are seriously affected by shorter periods of arterial block, and the brain is destroyed by even a few minutes of ischemia. Dogs' kidneys completely recover from two hours of total ischemia, and in 50 per cent of animals even after four hours of arterial block.²¹

The relations of juxtaglomerular tissue and renin are not known, possibly, the arterioles release a substance that activates renin precursor in the cortical epithelium. Renin escaping from the epithelial part of the juxtaglomerular apparatus, the

urine is quite low — only 0.08 per cent, as compared with 3.8 per cent for their work at the heaviest load. The rise in efficiency as work increases explains why, in the usual experiments on dogs and men, no relation between work and oxygen use can be detected.

It is not possible to measure the heat value for all the secretory work of the kidneys. Only the minimal possible amount is given by a study of urea concentration, but this is probably a considerable fraction of the total work. In any event, the extra oxygen consumed by the kidneys after changing from a low-protein to a high-protein

fever-producing substances even in infinitesimal traces.

There have been several reports on perfusion of human kidneys with physiologic saline solution or with serum, but when the rate of Diodrast clearance was measured it became obvious that the flow calculated by aqueous perfusion was only 10 to 20 per cent of the blood flow during life. By making sure that the renal vessels had passed out of rigor, and perfusing with oil, to avoid edema formation, Cox and Dock⁹ obtained in kidneys of young men rates of perfusion comparable with the most rapid rates observed when Diodrast was excreted during

TABLE 1 *Relation of Renal Osmotic Work* to the Oxygen Needs of the Rat and Its Kidney*

SUBJECT	OXYGEN UPTAKE		HEAT EQUIVALENTS	
	BY ANIMAL	BY KIDNEY	FOR RENAL OXYGEN	FOR OSMOTIC WORK ON UREA
	cc/min	cc/min	cal/min	cal/min
Control animal	4.0	0.21	1.05	00.0009
Animal fed 74 per cent casein diet	5.6	(0.22)	(1.10)	(00.0036)
Animal excreting 10 per cent urea	4.1	0.26	1.30	00.0500

*Work forced by feeding of urea and restriction of water intake.

intake is too small to be detected.⁴ This change of diet leads to hypertrophy of the kidneys, and after certain types of renal injury a high-protein diet may seriously jeopardize their recovery.⁵ Such a diet supplies not only urea but also aromatic acids, which the kidneys actively secrete five times as effectively as they filter off and concentrate urea.¹ It may well be that these aromatic acids stimulate hypertrophy and the increase in blood flow noted in kidneys at the onset of hypertrophy.⁶

The oxygen used by the rat's kidneys secreting 10 per cent urea is only 0.2 cc per gram per minute. The human kidneys probably never take up more than 0.1 cc per gram per minute,⁷ which could be supplied by a flow of 2 cc of normal blood, leaving the renal venous blood still 70 per cent saturated with oxygen. The rates of excretion of Diodrast and aromatic acids by human kidneys prove that the basal flow must be at least 4 cc per gram per minute. During the reaction to a pyrogen, such as typhoid vaccine, given intravenously the flow is almost 10 cc per gram per minute, even though fever is prevented by premedication with amidopyrin.¹ On the other hand, no significant rise in renal blood flow occurs with arterial anoxia due to high altitude or to low oxygen content of the alveolar air.⁸ The renal blood flow, which is many times greater than that necessary to supply the oxygen used by the kidneys, varies with the need to excrete substances noxious to the body. It is noteworthy that phenolic compounds are eliminated five times as efficiently as urea, and that maximal renal flow is evoked by

fever. This gave us a method for determining with some accuracy the effect of disease on the capacity of the vascular bed in various organs.

This method was applied, in 1939, to the study of the vascular bed of the kidneys in hypertension. At that time most of the outstanding investigators of renal physiology and pathology had enthusiastically or tentatively accepted the thesis that nearly all hypertensive patients had significant renal arteriosclerosis, and the corollary that nearly all hypertension was due to renal vascular disease.

In chronic uremia, whether due to pyelitis, nephritis or severe vascular disease, the perfusion rates were found to be low — less than 10 per cent of normal. Even in the absence of hypertension or uremia there was a decrease in the vascular bed with advancing age. But in the kidneys of hypertensive patients dying of stroke, coronary disease, heart failure or some intercurrent illness we usually found perfusion rates equal to those of normotensive subjects, and often as high as those of normotensive persons of the same age.⁹ We concluded, as have those who later determined flow during reaction to pyrogen in hypertensive patients, that in most cases the hypertension precedes any organic renal lesion.

The renal blood flow measured during life shows great fluctuations in normal subjects and even greater ones in many hypertensive persons. The true capacity of the renal bed can perhaps be measured only post mortem. The clinical fact of greatest importance is that hypertension is not

technic revealed in normal livers a capacity for flow well above the rates measured subsequently by Brainer and his colleagues²⁵ in men under basal conditions, using a catheter in the hepatic vein and a constant infusion of bromsulfalein.

Although anatomic studies indicate that the hepatic arterioles and the portal venules enter the sinuses of the liver lobule separately, the rate of perfusion through the normal portal vein drops a

patient with acute alcoholism whose liver weighed 3820 gm. in whom no cirrhosis had developed. It was our impression that portal perfusion was usually normal in cases with much perlobular scarring but with little fatty change or necrosis of the parenchyma (Table 3).

The capacity for hepatic arterial inflow, when portal flow was established, reached 1100 cc per minute in young normal subjects, 500 in old normal

TABLE 2 *Oxygen Needs of Tissues in the Intestine*

SUBJECT	OXYGEN UPTAKE				
	BY ANIMAL	BY HIND QUARTERS	BY LIVER AND GASTRO- INTESTINAL TRACT	BY KIDNEY	BY HEART
	cc / min	cc / min	cc / min	cc / min	cc / min
Control animal	4.0	0.25	0.9	0.2	0.4
Animal fed 74 per cent casein diet	5.6	0.45	2.3	0.2	(0.4)
Hyperthyroid animal	6.0	0.0	1.4	(0.5)	0.6

third when pressure in the hepatic artery is raised from 0 to 100 mm. during a double perfusion with oil, with portal inflow at 20 mm. In the livers of patients with alcoholic cirrhosis the portal flow fell, on the average, 78 per cent when flow at 100 mm. was established in the hepatic artery. This phenomenon was least marked in the cirrhotics not associated with chronic alcoholism, in which portal flow per gram fell, on the average, only 21 per cent. In many cirrhotic livers, decreases in portal perfusibility were noted when arterial pressure was 0. The lowest portal flow in a normal liver from an aged subject was 850 cc per minute corrected to

subjects and in patients with nonalcoholic cirrhosis, and rose to 1600 cc per minute in those with alcoholic cirrhosis, averaging 1360 cc in the last group. This is interpreted as confirming Herrick's²⁷ report of deranged portal-hepatic arterial ratios in cirrhosis. This is presumably due to the development of numerous minute arteriovenous fistulas analogous to the spider angiomas in the skin. The increased arterial flow is also borne out by the x-ray films of hepatic arterial beds injected post mortem with radio-opaque jelly (Figs. 3 and 4). The hyperplastic bed, which is most striking in alcoholic patients, is unusual in the others. Further information comes

TABLE 3 *Estimated Capacity for Blood Flow in Human Livers (Based on Perfusion with Oil Post Mortem)*

CONDITION OF LIVER	WEIGHT OF LIVER kg.	BLOOD FLOW			TOTAL cc / min
		HEPATIC ARTERY* cc / min	PORTAL VEIN† cc / min	PORTAL VEIN‡ cc / min	
Normal	1.6	800	1400	1000	1800
Fatty	5	700	180	~80	620
Cirrhotic (alcoholic)	2.1	1360	1000	270	1630
Cirrhotic (nonalcoholic)	2.2	550	1100	500	1450

*Pressure of 100

†Pressure of 20 with artery closed

‡Pressure of 20 with artery open

viscosity of blood, whereas in the cirrhotic liver with the poorest flow the rate was 480 cc. In two cirrhotic patients with enlarged livers the portal perfusibility was equal to the highest rate — 1700 cc per minute — in the liver of a normal young man. Loss of liver substance requiring a blood supply, scarring in portal areas and narrowing of sinuses by swelling of parenchyma may contribute to the decrease in portal perfusibility. The lowest perfusion rate, 180 cc per minute, was observed in a

from Dr. Roy Cohn,²⁸ who observed the portal pressure during laparotomy in 4 cases of advanced cirrhosis. On occlusion of the hepatic artery for a brief period, the portal pressure fell 21 to 29 per cent, or the equivalent of 7 to 11 cm. of water. During the operation, the systemic systolic arterial pressure was not over 80 in these desperately sick patients so that the effect of the hepatic arterial inflow was less than it would have been with normal levels of pressure. Even after occlusion of the

macula densa, may act on the glomerulus and cause efferent arteriolar constriction. The relation of this entire mechanism to chronic renal hypertension is obscure, for in the chronic disorder no circulating vasoconstrictor substance can be demonstrated. Increased vasoconstriction in chronic renal hypertension is certainly mediated through the central

diseased livers, and since no effect of such diets on renal metabolism has been demonstrated, the logical clinician would not reduce the protein intake in kidney disease. Experience has, of course, shown that in both hepatitis and cirrhosis a high-protein diet is beneficial, even though it makes the liver "work" harder. On the other hand, there is striking evidence that such a diet further injures kidneys in some species of animals with experimental nephritis, even though it does not appreciably increase the oxygen requirement of the kidneys.⁶

The blood flow of the liver in man is about 1 cc per gram per minute.²⁵ This supply comes from two sources, the portal vein, with a pressure equivalent to 10 to 20 mm of mercury, and the hepatic artery, with a pressure of 100 mm or higher. In man all the portal flow may be diverted into the inferior vena cava without damage to the liver, and



FIGURE 1 *The Glomerulus and Juxtaglomerular Tissue of a Normal Man Who Met a Sudden Death from Accident*

The macula densa (X-X) is a closely packed group of epithelial cells on the side of the distal convoluted tubule that touches the hilus of the glomerulus. The arteriolar cells, above and to the left of the lines, are shown by the arrow.

nervous system, but by humoral and not by reflex stimulation of the vasomotor center.²²⁻²⁴ When one recalls that minute quantities of pyrogen alter the "set" of the heat-regulating center, it is easy to believe that minute quantities of a substance from abnormal kidneys may alter the "set" of the vasomotor center.

THE LIVER

A kidney is the most marvelous anatomic structure in the body, its complexities being more awe inspiring than the thigh joints, which Solomon described as the "work of the hands of a cunning workman." The liver, on the contrary, is one of the simplest glandular structures in the body. Its oxygen uptake is determined by its metabolic activity, and in the rat rises from less than 0.1 cc per gram per minute on a protein-free diet to more than twice that amount on a diet with a 74 per cent protein content.⁴ The specific dynamic action of protein, or the rise in total metabolism after a protein meal, is due almost entirely to this intense hepatic activity (Table 2). The clinician, accustomed to prescribing rest for ailing men or organs, would predict that high-protein diets, by adding to metabolic activity, would retard recovery of



FIGURE 2 *Findings in the Kidney of a Man Who Lived for Five Days, in Severe Shock, after Injury*

The long, unusually cellular macula densa (X-X-X), and the large mass of cells in the arteriolar wall (arrow), are characteristic.

in dogs ligation of the hepatic artery causes no apparent damage. Such ligation may have serious effects on the liver in a patient with chronic biliary-tract disease. Arterial lesions are rare in the liver, as contrasted with the heart or kidney of man, and chief interest in the vascular bed of the liver is aroused by the severe vascular derangement seen in cirrhosis.

Few have questioned the relation between portal hypertension, with splenomegaly, esophageal varices and ascites, and a reduction in the portal bed by scar tissue. But no proof of such a reduction in portal bed had been offered, when, in 1941, the livers were perfused with oil post mortem.²⁶ This

mental pneumothorax³². They found that less than a fifth of the cardiac output went through the collapsed lung, and thus ended a controversy, based on indirect and conflicting evidence, that had lasted thirty years. They also utilized the procedure to demonstrate the increased cardiac output occurring with experimental arteriovenous fistulas³³. A flood of papers on the use of this method immediately followed, by 1930 Baumann had used the technic of ventricular puncture in man, and in 1941 Cournand and his co-workers began the catheterization of the right side of the heart that has opened a new chapter in the measurement of blood flow through the lungs in health and disease. By simultaneous measurement of right ventricular pressure the resistance offered by the pulmonary vascular bed can be measured. So far, no one has collected data, based on perfusion with oil post mortem, on the effect of varying degrees of collapse, distention and pulmonic pressure on the capacity of the vascular bed of the lungs of subjects of different ages and with various pulmonary lesions.

Although it is difficult to obtain quantitative data on collateral between the pulmonic and bronchial circulations by double perfusion, it has been possible to learn much by injection with radio-opaque or deeply colored jellies. Wood and his associates³⁴ in the Department of Pathology at Stanford University demonstrated extensive hyperplasia of the bronchial arterial bed and anastomosis with the pulmonary system in ulcerative tuberculosis, bronchiectasis and lung abscess, and in bronchogenic but not in metastatic cancer. At Cornell, anastomoses were demonstrated between the pulmonic and bronchial veins in normal adults, as well as extensive hyperplasia and varices in the submucous plexus of bronchial veins in cases of mitral stenosis³⁵. This established the source for the brisk hemoptysis that occurs in these patients with no evidence of infarction or intense pulmonary congestion.

Because the lungs occupy a large space and the blood circulates through them at a relatively low pressure, posture greatly alters the flow and the quantity of blood in the apex and base or in the dorsal and ventral parts. Posture also alters the volume flow of blood through the lung. On reclining, the blood that fills the veins below the diaphragm is no longer held back by gravity, and the effective venous pressure, the quantity of blood in the lungs and the output of the heart are increased, the last by as much as 30 per cent in some subjects.

The venous blood in the lungs must return to the left ventricle, which has its center of mass near the ventral chest surface and the diaphragm, slightly to the left of the midline. Because of the effect of gravity on this flow, venous pressure at the bases, expressed in its equivalent of water, is 20 to 30 cm. greater than that at the apex of subjects in the orthopneic position. When the patient is in the right semirecumbent posture, frequent with cardiac

patients, the venous pressure in the lateral and basal parts of the right lung is 10 to 20 cm. higher than that in any part of the left lung. These simple facts are of paramount importance in explaining the frequency of basal pulmonary edema and of right-sided hydrothorax in cases of cardiac failure, since the formation of tissue fluid increases rapidly with the rise in venous pressure³⁶.

The flow of lymph also increases with the rise in venous pressure and the dilution of toxic substances and the removal of bacteria or dusts such as silica, is most rapid and effective at the base of the lungs. At the apex, not only is the venous pressure low but also the arterial inflow is compromised when adults are sitting or standing. The systolic pressure in the right ventricle is 18 to 30 in recumbent subjects³⁷. It is perhaps only 12 to 25 when the patient is sitting, and the column of blood from the ventricle to the upper part of the lungs then exerts a pressure equally great. There is always a fall in pressure along the course of the arteries, and this must be more marked on the right side because the right pulmonary artery arises at an acute angle from the direction of flow in the pulmonic conus and pursues a tortuous path around the aorta. Consequently, the apical fourth of the left lung and the apical third of the right can have practically no blood flow for two thirds of each day in the life of sedentary people. Silica, coal dust, bacteria and toxins cannot be removed effectively when lymph flow ceases. Antibodies formed by the body or antibiotics given parenterally will not reach this zone. Oxygen tension will be high because aeration continues and the unsaturated blood from the systemic veins is not pumped up by the right ventricle. All this creates ideal conditions for tubercle bacilli, and it is not remarkable that in this region tuberculosis flourishes even when, in spite of positive findings in the sputum and constant seeding to all parts of the lung, no progressive lesion appears at the bases for many years^{38, 39}.

Although it is impossible to determine the relative significance of high venous pressures at the base and low arterial inflow at the apex in altering the resistance to tuberculosis, it is noteworthy that in rabbits and in cattle progressive lesions of tuberculosis are most numerous at a site anatomically opposite from the apex — namely, the dorsal and juxtadiaphragmatic part of the lower lobe^{40, 41}. Here, too, arterial inflow is reduced and venous pressure greatly lowered, since this portion of the lungs is highest above the heart in four-footed beasts. The high incidence of tuberculosis in cases of congenital pulmonary stenosis, which greatly lowers pulmonic arterial pressure, and the low incidence of active tuberculosis in mitral stenosis, with pulmonic pressure two to six times normal,³⁷ strongly support the thesis that arterial inflow is of crucial importance. The effect of gravity on the lungs thus explains the remarkable efficacy of rest

hepatic artery, however, the portal pressure did not fall to normal in any of these cases, so that arteriovenous fistulas were not the main cause of portal hypertension

I have seen only 2 cases of Banti's disease accompanied by portal hypertension without portal or splenic thromboses and with histologically normal

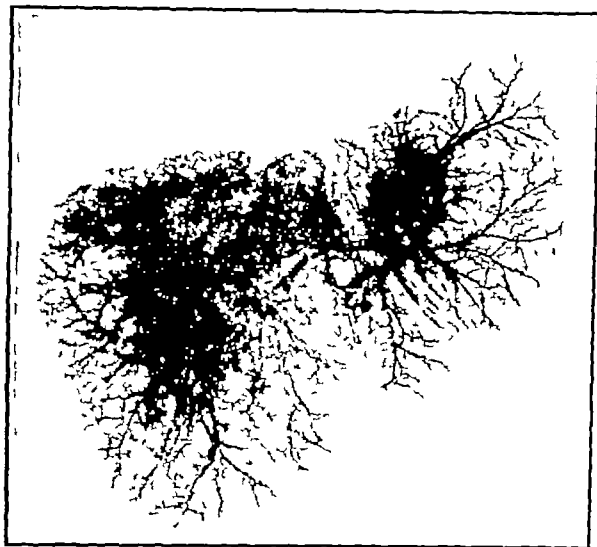


FIGURE 3 *Hepatic Arterial Bed, after Lead-Gelatin Injection, in the Normal Liver, as Visualized by X-rays*

livers. The only conceivable explanation is a congenital defect in the communications of the portal and hepatic arteries, with telangiectasia in the lobules. This could be determined during life by the fall of portal pressure to normal on occlusion of the hepatic artery, and post mortem by double perfusion or even by hepatic arterial injection. So far, no such studies have been reported.

To what extent hepatic arterial flow is increased in chronic portal hypertension in various types of cirrhosis can best be determined by observations made during operations to provide portocaval anastomosis. When such arteriovenous fistulas are important factors, a complete portocaval shunt is obviously preferable to one between the splenic and the renal vein, for the latter does not close off the leak between the artery and the portal vein. It is to be hoped that surgeons will soon provide data on the fall of portal pressure with arterial occlusion in various types of liver disease, and especially in the Banti syndrome. In this connection one recalls the following comment of Sir Thomas Lewis²⁹

Surgeons, if they would, could contribute heavily to clinical science. The special opportunities for observation presenting themselves during the progress of operations may be noted, they are not utilized as they might be. Such investigations must remain purely incidental, and must always be conducted within strictly prudent bounds.

Another anomaly of the hepatic circulation that occurs in dogs — but not in cats, rodents, herbivora or man — is worth notice, since it has led to some interesting confusion in pharmacologic study. The dog has a muscular sphincter at the outlet of the hepatic vein, and spasm of this sphincter, evoked by histamine³⁰ and to a lesser degree by digitalis,³¹ leads to a pooling of blood in the liver and portal bed, a fall in the systemic venous pressure and a marked reduction in cardiac output. Digitalis causes a fall of venous pressure and cardiac output in normal men, but the decrease is much less striking than that in dogs. In describing the hepatic element in the dog's response to digitalis, Tainter

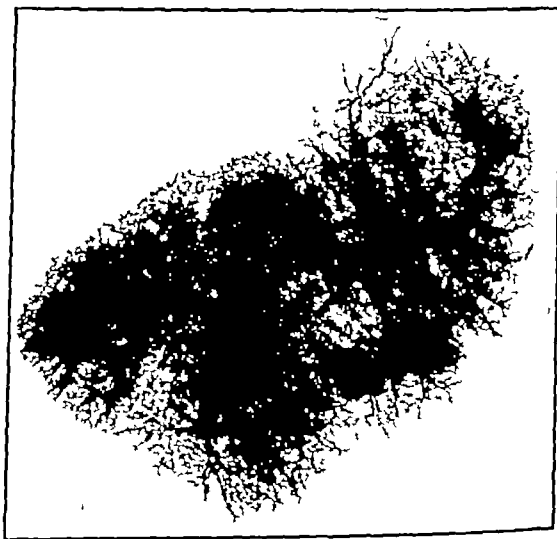


FIGURE 4 *Hepatic Arterial Bed from a Chronic Alcoholic Patient with Portal Cirrhosis. Note the extensive hyperplasia*

and Dock³¹ took pains to point out that no such action could be postulated as contributing to the effect of digitalis in cardiac failure in man.

THE LUNGS

The blood flow through the lungs was the first to be measured. In 1870 Fick pointed out that by division of the oxygen uptake or carbon dioxide output by the difference in gas content of blood from the right and left sides of the heart the flow through the lungs could be determined. This was actually done, in dogs, sixteen years later by Gréhant and Quinquaud and in horses during exercise, rest and digestion by Zuntz.

Up to 1923 this technic had not been used in North America, nor had it been employed to study the effects of disease. In that year two house officers at the Peter Bent Brigham Hospital used this method to measure the blood flow through the collapsed lung and the opposite lung in experi-

mental pneumothorax³². They found that less than a fifth of the cardiac output went through the collapsed lung, and thus ended a controversy, based on indirect and conflicting evidence, that had lasted thirty years. They also utilized the procedure to demonstrate the increased cardiac output occurring with experimental arteriovenous fistulas³³. A flood of papers on the use of this method immediately followed, by 1930 Baumann had used the technic of ventricular puncture in man, and in 1941 Cournand and his co-workers began the catheterization of the right side of the heart that has opened a new chapter in the measurement of blood flow through the lungs in health and disease. By simultaneous measurement of right ventricular pressure the resistance offered by the pulmonary vascular bed can be measured. So far, no one has collected data, based on perfusion with oil post mortem, on the effect of varying degrees of collapse, distention and pulmonic pressure on the capacity of the vascular bed of the lungs of subjects of different ages and with various pulmonary lesions.

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flat in bed in the treatment of apical tuberculosis, as contrasted with miliary or other types of the disease. It should be noted that antibiotics will be least effective in reaching apical lesions when patients are allowed to sit up most of the day, so that the type of management introduced by Joseph Pratt will continue to be of value even after effective chemotherapy for tuberculosis has been developed.

The peculiar relations of the pulmonary circulation to the gravitational pull are of great practical effect in the management of both congestive failure and pulmonary tuberculosis—the two most frequent natural causes of death between childhood and senescence. In heart failure the orthopneic posture makes life tolerable, in apical tuberculosis it may make recovery impossible.

THE HEART

The oxygen requirements of the isolated hearts of rats, dogs and other mammals have been measured, as have the coronary flows in several species and in the human heart revived after death. In the rat, the oxygen used by the heart even in the hyperthyroid state with pulse rates over 300 is not over 0.6 cc per gram per minute.⁴² The oxygen used by the human heart probably never exceeds 0.1 cc per gram per minute and is believed to be about 0.06 cc during vigorous activity. That quantity can be supplied by a blood flow of 1 cc per minute, which leaves the venous blood still half saturated with oxygen. This maintains an oxygen tension adequate to allow diffusion of oxygen into the center of a muscle fiber twice the diameter of those in a greatly hypertrophied heart.

Cardiac hypertrophy is a mechanism of great adaptability. In arterial hypertension of gradual evolution the wall of the left ventricle becomes thicker, but the diastolic capacity does not increase, the fibers are thicker but no longer than normal.⁴³ But when increased output must be maintained, as in hyperthyroidism, anemia or valvular disease, the fibers grow longer, and the chamber becomes more capacious. Loss of efficiency, the usual cause of heart failure, leads to an increase in both length and thickness of the fibers. Hypertrophy occurs rapidly, and when the stimulus is removed the muscle returns quickly to its normal weight.⁴⁴ One of the problems of great importance to the cardiologist is whether the coronary bed adapts itself to the growth of the myocardium with the same nicety as the muscle fibers adapt themselves to the load imposed on them. Several authors have suggested that congestive failure occurred because hypertrophy outstripped the growth of the coronary bed. Kountz,⁴⁵ perfusing revived human hearts, observed control rates of flow up to 3 cc per gram per minute under vasodilator drugs. He found the rates low in hearts revived after death from cardiac

failure, but in such hearts only low perfusion pressures could be maintained.

The perfusion of hearts with oil has yielded decisive data, and in this case the data so far have not been supplemented even by the wielders of the vascular catheters. There has, of course, never been any doubt that occlusion or severe narrowing of the large coronary arteries that lie in the epicardium must reduce the flow to the heart muscle. The only perfusion rates below 0.7 cc per gram per minute, calculated as blood flow at the equivalent of 100 mm of mercury, were observed in hearts with severe coronary atherosclerosis, the lowest rate, 0.2 cc per minute, was in a heart with two large arteries occluded and constricted regions in most epicardial branches. In hypertrophy without coronary disease the flow rates were more than adequate to provide oxygen in excess of the needs of the thickest fibers.⁴⁶

As hearts grow from infancy to maturity the coronary perfusibility per gram of tissue decreases. After maturity, the average perfusibility of heart of normal weight decreases. The flow at ages sixty-six to eighty-five was 30 per cent less than that at ages twenty-five to forty. In hypertrophied hearts the flow per gram also decreases, but this appears merely as a smooth extension of the curve of the decline in the normally growing heart up to maturity. Even in the largest hearts of old men, where the main branches were patent the flow at 100 mm never fell below 0.7 cc per gram per minute. At the patient's usual diastolic pressure, the calculated flow fell below that level in only 2 cases of aortic insufficiency. Neither in the heart with the lowest calculated flow—0.45 cc at the patient's diastolic pressure—nor in any of the others had there been angina during life or fatty change in the myocardium post mortem.⁴⁶ These are the classic symptomatic and anatomic sequelae of cardiac anoxia, whether due to coronary disease or severe anemia.

Anatomic studies had given an equivocal answer to the question of coronary flow in cardiac hypertrophy. Injection of the arteries by Schlesinger's technic demonstrates a striking hyperplasia of the visible arteries, whereas capillary counts show no reduction in loops per fiber, and a decrease in capillary loops per gram of muscle.⁴⁷ It should be recalled that resistance to flow decreases as the fourth power of the radius of the vessel increases. Thus a 10 per cent increase in diameter of the minute vessels would cause an increase of nearly 50 per cent in flow, a 19 per cent increase would double it. Changes in caliber unperceived by the anatomist may greatly alter the perfusibility of an organ such as the heart, and the only real test of perfusibility is perfusion.

Perfusion shows that the possible flow in the heart of a healthy young man may be as much as 500 cc per minute, whereas in the hearts of older patients with hypertension the ventricles, two or three times

heavier, have possible rates of flow of 700 to 1000 cc. The coronary bed adapts itself to the needs of the organ it serves, as would be expected from the development of the vasculature in other sites — around the coarcted aorta, in the pregnant uterus and even in tumors. Having seen the intercostal arteries, many centimeters away from the tissue that needed blood, so dilated as a result of coarctation that the ribs themselves became eroded,⁴⁸ one would be surprised if the arteries in the myocardium could not hypertrophy to provide blood needed by hypertrophied muscle or by a region supplied by an occluded coronary branch.

The coronary bed is peculiarly liable to atherosclerosis, at least in populations with dietaries such as ours. Nearly a fifth of the sedentary men of North America die because of the vulnerability of the epicardial branches of the coronary system. Even in manual workers and elderly women the death rate from coronary disease is high. Occlusion may occur when the aorta and the rest of the arteries are in faultless condition, particularly in men under the age of fifty.⁴⁹

Even at birth these arteries have intimal layers thicker than those of any other vessels of similar size in the body, and this natural intimal thickness increases throughout life even if atherosclerosis fails to occur. In a small series, male infants were found to have far more striking intimal cushions than females.⁵⁰ Perhaps the earlier onset of disease and far higher mortality in males is due to this anatomic peculiarity. Men also drink more milk and eat more eggs than women, but the frequency of gallstones in women in North America makes it unlikely that the sex difference is due to lower blood cholesterol levels. In the Orient coronary disease and cholesterol stones are rare; there, men have more gallstones (of the calcium bilirubinate type) than women do.⁵¹ It may be concluded that atherosclerosis will occur in people with meat and dairy products in the regular diet, its predilection for the coronary arteries, in men and in certain families, may be due to an anatomic anomaly present at birth.

Using the oil perfusion technic and also glass microspheres of various sizes, Prinzmetal and his co-workers⁵²⁻⁵⁴ have studied the volume of collateral flow and the caliber of the cross channels in the heart. This has given further evidence of the adaptability of the coronary circulation under the stresses imposed by disease. Because of this adaptability normal cardiac function may be maintained for years after the occlusion of the largest arteries in the heart.

* * *

This description of the circulatory peculiarities of some of the viscera has emphasized the phases of investigation with which I am most familiar. The introduction of the vascular catheter and the use

of radioactive isotopes have opened up a vast program of study of the circulation in various organs of normal and of diseased men, and the description of this problem will be greatly modified in the next decade. Yet it is instructive to see that much can still be learned by the use of simple methods of post-mortem study and animal experiment.

Perfusion with oil serves to measure the capacity for flow through many organs. Perhaps the most urgent problem connected with the study of aging is the disseminated cortical atrophy that is associated with loss of memory, originality and judgment. Methods for measuring the cerebral flow during life are now being perfected, but by perfusion it is possible to measure flow through each major subdivision of the cerebral vascular bed and to correlate changes with the histology of the brain and with clinical observations on cerebration and total cerebral flow. It is to be hoped that this method will be applied in all clinics where blood flow is being measured during life. In most such centers post-mortem material from patients who have been subjected to elaborate quantitative studies is being examined exactly as it might have been in the days of Virchow or Rokitsanski.

During the last year of a life largely devoted to bettering the care of the sick and the education of physicians, George Cheyne Shattuck made a generous gift for the purpose of improving the teaching of morbid anatomy at Harvard. This eminent practitioner from his own experience and from the work of such contemporaries as Bright and Addison, fully realized the supreme value of complete post-mortem examination correlated with well planned clinical study. New methods for clinical study merely make more essential the evolution of a morbid anatomy adequate to maintain this effective correlation. Even with the use of methods available to all for the past seventy years, it is possible for pathologists and even practitioners to make essential contributions to an understanding of the diseases that remain the "captains of the men of death."

REFERENCES

1. Smith H. W. Physiology of renal circulation. *Harv. Lectures* 35: 166-222, 1940.
2. Phillips R. A., Dole V. P., Hamilton P. B., Kendall E. Jr., Archibald R. M., and Van Slyke D. D. Effects of acute hemorrhagic and traumatic shock on renal function of dogs. *Am. J. Physiol.* 145: 14 (1946).
3. Dock W. Rate of oxygen utilization by rat kidneys at different rates of urea excretion. *Am. J. Physiol.* 106: 745-749, 1933.
4. *Idem*. Relative increase in metabolism of liver and of other tissues during protein metabolism in rat. *Am. J. Physiol.* 97: 117-125, 1931.
5. Farr L. E. and Smadel J. E. Effect of dietary protein on course of nephrotoxic nephritis in rats. *J. Exper. Med.* 70: 615-627, 1939.
6. Dock W. and Rivland D. A. Renal blood flow after subtotal nephrectomy. *Proc. Soc. Exper. Biol. & Med.* 36: 196-198, 1939.
7. Cutting M. and McCance R. A. Metabolism of kidney slices from new born and mature animals. *J. Physiol.* 105: 205-214, 1946.
8. Dole V. P., Emerson K. Jr., Phillips R. A., Hamilton P. B., and Van Slyke D. D. Renal extraction of oxygen in experimental shock. *Am. J. Physiol.* 145: 337-345, 1946.
9. Cox A. J. Jr. and Dock W. Capacity of renal vascular bed in hypertension. *J. Exper. Med.* 74: 167-175, 1944.
10. Sellkurt E. E. Renal blood flow and renal clearance during hemorrhagic shock. *Am. J. Physiol.* 145: 699-703, 1946.

11 *Idem* Changes in renal clearance following complete ischemia of kidney *Am J Physiol* 144 345-403, 1945

12 Bruns, C, Knudsen E O E, and Raaschou, F Kidney function and circulatory collapse post syncope oliguria *J Clin Investigation* 25 568 574 1946

13 Raska, S B Metabolism of kidney in experimental renal hypertension concentration of cytochrome c and activities of cytochrome oxidase and of succinic dehydrogenase systems in kidney of dogs with experimental renal hypertension Inhibitory effect of renin and of kidney tissue preparations on respiratory enzymes *J Exper Med* 82 227-240 1945

14 Pickering, G W and Prinzmetal M Effect of renin on urine formation *J Physiol* 98 314-335, 1940

15 Goormaghtigh N Existence of endocrine gland in media of renal arteries *Proc Soc Exper Biol & Med* 42 688, 1939

16 Goormaghtigh, N, and Grimson, K S Vascular changes in renal ischemia cell mitosis in media of arteries *Proc Soc Exper Biol & Med* 42 227 1939

17 Dunihue, F W Effect of bilateral adrenalectomy on juxtaglomerular apparatus *Anat Rec* 94 379, 1946

18 Dock, W Unpublished data

19 Goormaghtigh, N Facts in favour of endocrine function of renal arteries *J Path & Bact* 57 392, 1945

20 Taquini, A C, and Fasciolo, J C Renin in essential hypertension *Am Heart J* 32 357-363, 1946

21 Phillips, R. A, and Hamilton, P B Duration of renal ischemia required in dogs to produce damage of lethal degree *Federation Proc* 5 (Part 2) 80 1946

22 Dock, W, and Rytand, D A Absence of vasoconstrictor substance in blood of rats with renal hypertension *Proc Soc Exper Biol & Med* 32 374, 1934

23 Dock W Vasoconstriction in renal hypertension abolished by pithing *Am J Physiol* 130 1 8, 1940

24 Dock, W, Shidler, F P, and Moy B Vasomotor center essential in maintaining renal hypertension *Am Heart J* 23 513 521 1942

25 Bradley, S E Ingelfinger F J Bradley, G P and Curry J J Estimation of hepatic blood flow in man *J Clin Investigation* 24 890-897, 1945

26 Dock, W Role of increased hepatic arterial flow in portal hypertension of cirrhosis *Tr A Am Physicians* 57 302-306, 1942

27 Herrick F C Experimental study into cause of increased portal pressure in portal cirrhosis *J Exper Med* 9 93 104 1907

28 Cohn, R Personal communication

29 Lewis T *Clinical Science Illustrated by Personal Experiences* 189 pp London Shaw and Sons, 1934

30 Bauer, W, Dale, H H, Poulsen, L T, and Richards D W Control of circulation through liver *J Physiol* 74 342-375, 1932

31 Tainter, M L, and Dock, W Further observations on circulatory actions of digitalis and strophanthus with special reference to liver, and comparisons with histamine and epinephrine *J Clin Investigation* 8 485 504, 1930

32 Dock, W, and Harrison, T R Blood flow through lungs in experimental pneumothorax *Am Rev Tuberc* 10 534-539 1925

33 Harrison, T R Dock W and Holman, E Experimental studies in arterio-venous fistulae cardiac output *Heart* 11 337 341, 1924

34 Wood, D A, Crever J W, and Miller M Changes in dual circulation of human lungs in various pathological conditions. *J Tech Methods* 17 78 90, 1937

35 Ferguson, F C, Kobalak R E, and Deitrick, J E Varices of bronchial veins as source of hemoptysis in mitral stenosis. *Am Heart J* 28 445-456 1944

36 Dock W Anatomical and hydrostatic basis of orthopnea and of right hydrothorax in cardiac failure *Am Heart J* 10 1047 1055 1935

37 Bloomfield, R A, Lauson H D, Courmand, A, Breed, E S, and Richards, D W, Jr Recording right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of cardiorespiratory disease *J Clin Investigation* 25-639-664, 1946

38 Dock, W Apical localization of phthisis its significance in treatment by prolonged rest in bed *Am Rev Tuberc* 53 297 305, 1946.

39 *Idem* Reasons for common anatomic location of pulmonary tuberculosis *Radiology* (in press)

40 Medlar, E M, and Sasano K T Study of pathology of experimental pulmonary tuberculosis in rabbit *Am Rev Tuberc* 34 456-476, 1936

41 Medlar, E M Pulmonary tuberculosis in cattle location and type of lesions in naturally acquired tuberculosis. *Am Rev Tuberc* 41 283 306, 1940

42 Dock, W, and Lewis, J K Effect of thyroid feeding on oxygen consumption of heart and of other tissue *J Physiol* 74 401-406, 1932

43 Rytand D A, and Dock, W Experimental concentric and eccentric cardiac hypertrophy in rats *Arch Int Med* 56 511 520, 1935

44 Drury, A N Observations relating to cardiac hypertrophy produced in rabbit by arterio-venous anastomosis effect of closure of anastomosis *Quart J Exper Physiol* 33 107 112, 1945

45 Kountz, W B, and Smith, J R. Flow of blood in coronary arteries in pathological hearts *J Clin Investigation* 17 147 152, 1938

46 Dock, W Capacity of coronary bed in cardiac hypertrophy *J Exper Med* 74 177-186 1941

47 Wearn, J T Morphological and functional alterations of coronary circulation *Harvey Lectures* 35 243-270, 1940

48 Railsback, O C, and Dock, W Erosion of ribs due to stenosis of isthmus (coarctation) of aorta. *Radiology* 12 58-61, 1929

49 French, A J, and Dock W Fatal coronary arteriosclerosis in young soldiers *J A M A* 124 1233 1237, 1944

50 Dock, W Predilection of atherosclerosis for coronary arteries. *J A M A* 131 875-878, 1946

51 Snapper, I *Nutritional Problems in the Orient* Vol. 2 *Advances in Internal Medicine* New York Interscience Press (in press)

52 Prinzmetal, M, Kayland, S, Margoles C, and Tragerman, L J Quantitative method for determining collateral coronary circulation preliminary report on normal human hearts *J Mt Sinai Hosp* 8 933 945 1942

53 Prinzmetal, M Collateral circulation of human heart *Mod Concepts of Cardiovascular Disease* 15 No 10 October, 1946

DWARFISM IN HEALTHY CHILDREN ITS POSSIBLE RELATION TO EMOTIONAL, NUTRITIONAL AND ENDOCRINE DISTURBANCES*

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CHILDREN in good health who are receiving an adequate diet tend to follow a relatively standard pattern of growth and maturation. Although moderate deviations from the average trend are commonly considered to be normal physiologic vari-

intestinal, renal, hepatic, skeletal or endocrinologic system. There remained, however, a group of 28 boys and 23 girls, two and a half to fifteen years of age, in whom no such abnormality could be found. The present paper is the result of attempts to dis-

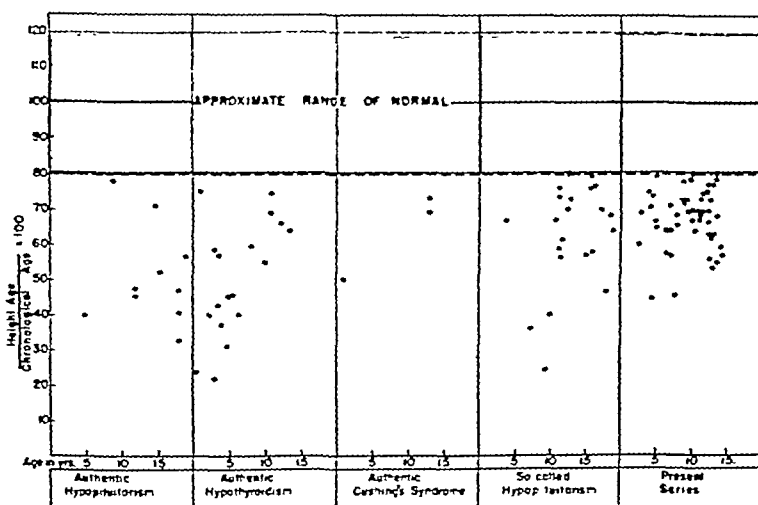


FIGURE 1 Heights of Various Types of Dwarfed Children

Results are expressed as height age divided by chronological age times 100 (ordinate) and are plotted against approximate chronological age (abscissa). A height-age ratio of 100 indicates that the subject is of average normal height for the age and sex. The shaded area gives the approximate range of normal.

ations, extreme deviations suggest that some abnormality exists. In the past few years more than 100 abnormally short children have been encountered in the pediatric clinics of this hospital. In approximately 50 per cent of these patients the stunted growth could be related to a definite disturbance in the pulmonary, cardiovascular, gastro-

cover and eradicate the cause of stunted growth in such patients.

Description of Patients

Figure 1 presents the data on the stature of these patients and gives comparative information on the height of patients dwarfed as the result of authentic hypopituitarism,¹⁻¹¹ hypothyroidism¹² and Cushing's syndrome¹²⁻¹⁶ respectively. A number of the so-called "pituitary dwarfs" of the literature are also represented.¹⁶⁻²⁵ The results are expressed in terms of height age times 100 divided by actual age, the height age of each subject being the average age of normal children of the same height and sex.²⁶ None of the patients under discussion had a height age that was more than 80 per cent of the actual age. Expressed in another manner, all the present subjects were 5 cm. or more shorter than 90 per cent of

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†This work was supported in part by a grant from the Commonwealth Fund, New York City, in part by a grant from the Permanent Charity Fund of Boston, and in part by a grant from the James Foundation, New York City.

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normal children of the same sex and age. It can also be seen that the patients were approximately as short as those with authentic endocrine dwarfism and that they were no taller than most of the so-called "pituitary dwarfs" of the literature.

Information on the stature of the parents and siblings of these patients may be of interest. Data on

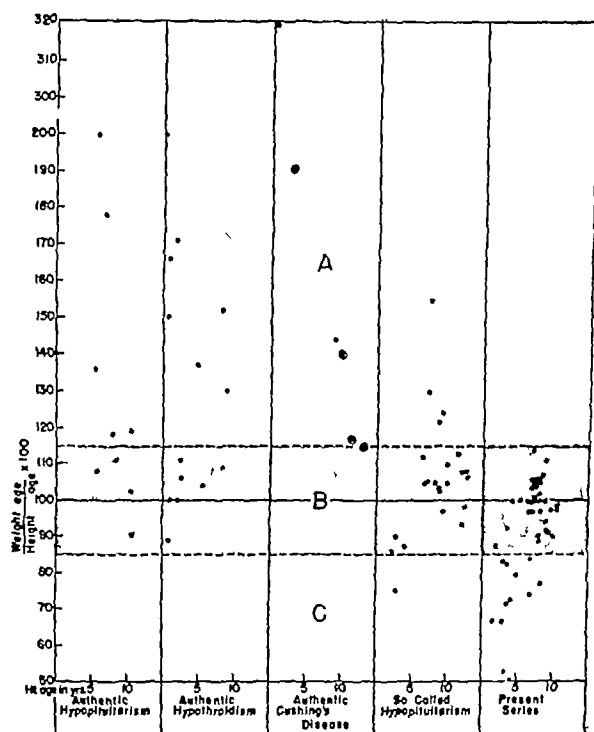


FIGURE 2 *Weight Relative to Height of Various Types of Dwarfed Children*

Results are expressed as weight divided by height age times 100 (ordinate) and plotted against height age (abscissa). The upper clear area (A) includes patients considered to be overweight for their height, the shaded area (B) suggests that the weight is within normal limits for height, the lower clear area (C) includes patients who are underweight for height. The circled points represent children with Cushing's syndrome who were not dwarfed³⁰ and so emphasize the fact that there is a tendency to be overweight in this condition.

the height of the parents were available in 39 of 51 cases. In 74 per cent the father was reported to be more than 158 cm and the mother more than 152 cm tall. Nineteen patients had younger siblings, 84 per cent of whom were as tall as or taller than the patients. In only 5 per cent of cases were there close relatives whose stature was reported to be remarkably short. This information appeared to provide little justification for the assumption that the small stature of the children was necessarily due to hereditary limitation of growth capacity.

Figure 2 gives information concerning the weight of these patients. To relate their weight to their height, the results are presented as weight age

times 100 divided by height age. A ratio of 85 to 115 is considered to be approximately within normal limits (Fig 2, Group B). Higher ratios suggest that the subject is overweight (Fig 2, Group A), whereas lower ratios suggest that he is underweight (Fig 2, Group C) for his height. The values presented indicate that about 70 per cent of the patients in the series belonged to Group B, the remaining 30 per cent were underweight (Group C). In contrast, the patients with authentic endocrine dwarfism tended to be of at least average normal weight for height (a weight-age ratio of more than 100), and about half—those in Group A—were overweight (a ratio of more than 115) according to this definition.

The weight of a child relative to his height is not always an adequate index of the subcutaneous fat stores.^{31, 32} Thus, although there was a tendency for the patients who were relatively more underweight to be thin, clinical examination indicated that all but 3 of the children whose weight was within normal limits for height also tended to have scanty subcutaneous tissue stores (Fig 3).

Figure 4 presents information concerning the skeletal maturation of the various types of patients. The skeletal age was estimated from roentgenograms of the hand and wrist according to Todd's standards. The results are expressed in the following ratio: skeletal age times 100 divided by actual age. It is evident that the skeletal age of the majority of the patients was retarded behind the actual age to approximately the same degree as the height age. In this respect the patients did not differ consistently from the authentic endocrine or the so-called "pituitary dwarfs." There was, however, a tendency for the hypothyroid children to show the greatest and those in the present series and the so-called "hypopituitary patients" the least degrees of retardation in skeletal maturation.

Nutritional History

Since it did not seem appropriate to explain the small stature of these patients a priori by a hereditary limitation in growth capacity and because no physical diseases could be discovered, the average daily food intake of 29 patients was evaluated by means of detailed dietary histories obtained through procedures described elsewhere.³³ The results are considered below from two points of view: the average daily caloric intake and the average intake of certain building materials—namely, protein and calcium. Generally speaking the nutritional histories of the majority of these children indicated clearly that they were difficult feeding problems and had been so for the major portion of their lives, in many cases since infancy.

Caloric intake. Figures 5 and 6 present values for the estimated average caloric intake of each of the girls and boys on whom nutritional histories were obtained. In these figures the continuous curves

running upward from left to right represent the average caloric intake of normal children of corresponding ages, whereas the interrupted curves stand for a standard deviation below the average and approximate the lower limit of normal for this community.^{21, 22} It can be seen that the caloric intake of 85 per cent of the patients was at or below the lower limit of normal for chronologic age. These

Protein intake Figure 7 sets forth estimations of the average daily protein intake in the cases in which nutritional histories were obtained. The continuous curve running upward from left to right represents the protein allowances for boys recommended by the Food and Nutrition Board of the National Research Council, the same curve gives the recommended allowances for girls up to eleven years,

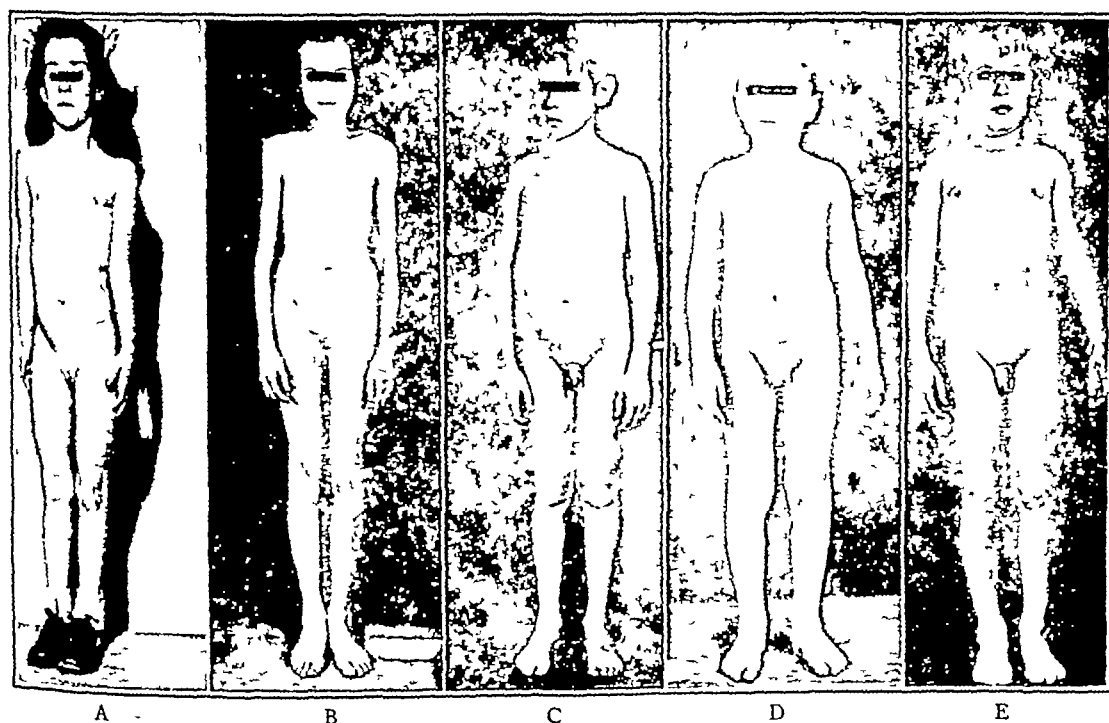


FIGURE 3 Physical Appearance of Various Types of Dwarfed Children

Patient A, aged six and a half years, was underweight for her height (Group C, Fig. 2) and was very thin. Patient B, aged thirteen and a half years, was an extremely thin member of Group B (weight within theoretical normal limits for height). Patient C, aged twelve and a half years, was of normal weight for his height (Group B) and appeared to be adequately nourished. Patient D, aged eleven years old, was overweight for his height (Group A) and was moderately obese. Patient E, aged twelve years and an example of authentic hypopituitarism, was a member of Group A and was moderately obese.

data, however, do not take into consideration the influence of subnormal size on caloric requirements. Presumably, the requirements should be scaled down somewhat to correct for the fact that these patients had a smaller protoplasmic mass and surface area than normal children of the same age. On the other hand, the caloric requirements may easily have been greater than those of normal children of the same size or height to enable them to catch up to normal and to meet the larger caloric requirements for activity reported for older children.²⁶ When such variables as these are considered, it seems reasonable that the trends shown in Figures 5 and 6 are valid. Certainly, they are in keeping with the clinical observation that the majority of the children had poor subcutaneous fat stores.

whereas the interrupted line at the right indicates allowances for older girls. The values were lower on the average than the allowance for age recommended by the National Research Council. When calculated in relation to body weight, however, the average daily intake of protein of these patients was 2.2 gm per kilogram of body weight, with a range of 1.5 to 3.6 gm. There was essentially no difference between the average daily values found for children of normal weight (Group B, 2.1 gm per kilogram of body weight) and those for underweight subjects (Group C, 2.4 gm).

There is evidence that children can grow — that is, they can be in positive nitrogen balance — when the daily intake of protein is as little as 0.7 gm per kilogram of body weight.²⁷ In this connection it is

of interest that the daily increase in body protein during the major part of childhood amounts to only

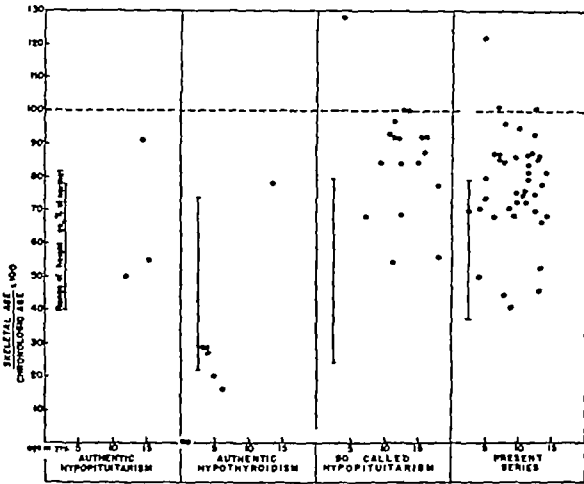


FIGURE 4 Skeletal Development of Various Types of Dwarfed Children.

The results are expressed as skeletal age divided by chronologic age times 100 (ordinate) plotted against chronologic age (abscissa). The vertical lines in each section indicate the range of height ages divided by chronologic ages times 100 shown in Figure 1. The interrupted horizontal line indicates where the bone age (and height age) plots would fall if they corresponded to the average normal for sex and age.

about 0.1 gm per kilogram of body weight.¹² Viewed in this light, a daily protein intake of ap-

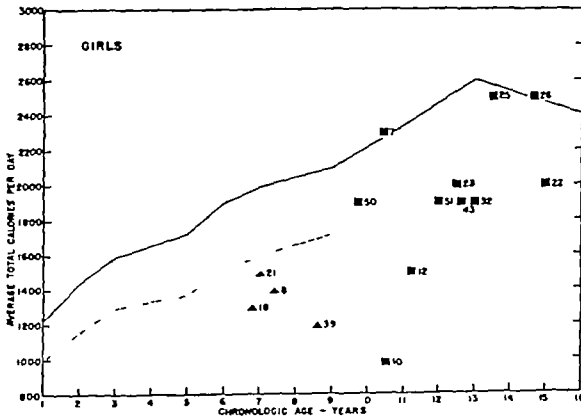


FIGURE 5 Average Total Daily Caloric Intake for Girls (ordinate) Plotted against Chronologic Age (abscissa).

The squares stand for children of normal weight for their height (Group B, Fig. 2), and the triangles represent children who were underweight for their height (Group C, Fig. 2). The numbers adjacent to these symbols are case numbers. The continuous curve running upward from left to right gives the approximate average normal total caloric intake for children of corresponding age and sex. The lower interrupted curve is one standard deviation below the average normal and gives the approximate lower limit of normal. These normal data for children one to nine years of age are based on data of Beal, Burke and Stuart¹⁴; the data for children older than nine years are National Research Council daily allowances modified to fit the fact that girls have their maximum growth spurt and hence caloric requirements at thirteen years, whereas boys have theirs at about fifteen years.

proximately 2 gm per kilogram of body weight is apparently in excess of minimum growth requirements.

Evaluation of the adequacy of the protein intake, however, also demands simultaneous consideration of the caloric intake. The primary nutritional re-

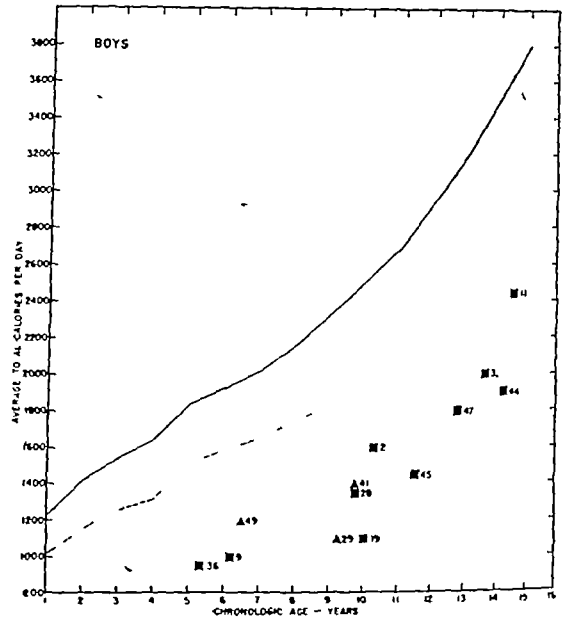


FIGURE 6 Average Total Daily Caloric Intake for Boys Plotted against Chronologic Age.

The legend of Figure 5 explains the chart.

quirement of the body is for calories to meet the energy requirement. When the caloric balance becomes negative, there is an increased tendency for

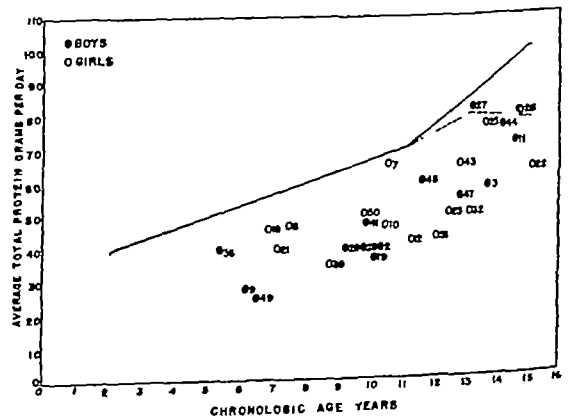


FIGURE 7 Average Total Daily Protein Intake for Boys and Girls Plotted against Chronologic Age.

The continuous curve running upward from left to right gives approximately the allowance recommended by the National Research Council for boys. The same curve gives values for girls up to eleven years, and the interrupted line at the right-hand end of the continuous curve gives values for older girls.

dietary protein to be used for fuel rather than for growth. Thus, a protein intake that is ample for growth under conditions of caloric adequacy may be

insufficient under conditions of caloric inadequacy. Consequently, it seems probable that in our patients, the protein intake per se was not incompatible with growth, but that it may have been rendered inadequate by the poor caloric intake.

Calcium intake Calcium as a limiting dietary factor was also considered. In 18 of the 29 subjects the intake of this mineral was more than the daily minimum requirement of 600 to 800 mg for children of preschool age.³³ The remaining 11 patients were found to be taking 200 to 600 mg daily. It should

intake of the 11 children receiving a total of 600 mg or less per day was 22 mg per kilogram of body weight — the range being 10 to 35 mg. It is of interest that growing children habituated to a low-calorie diet can store in their bodies as much as 89 per cent of a small calcium intake — 200 to 250 mg per day.⁴⁰ These facts suggest that a small child receiving 200 mg of calcium per day can absorb and retain 175 mg, which exceeds normal growth requirements for such a child. Although it is difficult to draw more than tentative conclusions from such

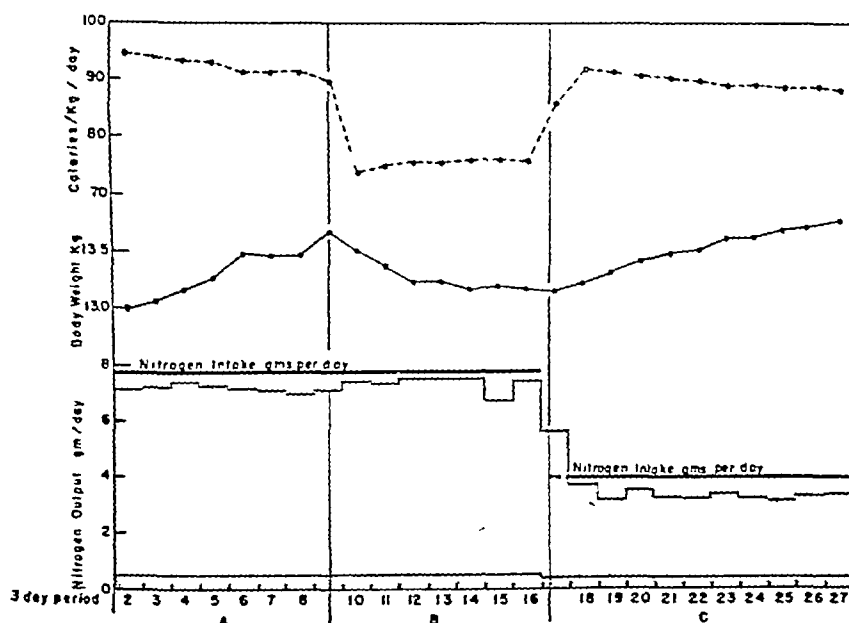


FIGURE 8. Changes in Body Weight and Nitrogen Balance Induced by Variations in Caloric Intake in a Thin, Underweight Dwarfed Child (Patient A, Fig 3)

In the upper portion of the chart, the caloric intake per kilogram per day is indicated by hollow circles connected by an interrupted line. The black circles connected by a solid line represent body-weight measurements. In the lower portion of the chart are set forth nitrogen-balance data. The distance from the baseline to the double horizontal line gives the nitrogen intake. The cross-hatched area adjacent to the baseline gives the nitrogen output in the stool, and the vertically lined area above this gives the output in the urine. The balance is indicated by the distance between the intake and the urine plus stool output.

be mentioned that the recommended allowance for calcium increases with age through the peak of the adolescent growth spurt and that these children ranged in chronologic age between two and fifteen years. It may also be stated that the minimum allowances referred to above were recommended for subjects whose stores were already saturated. It has been calculated that the daily calcium growth of normal children amounts to between about 5 and 7.5 mg per kilogram of body weight.³⁹ Expressed in terms of total retention per day, this amounts to approximately 68 mg in normal four-year-old subjects and increases to a maximum of 190 mg in normal sixteen-year-old children. The average daily

observations, the foregoing information indicates that few, if any, of the patients had a calcium intake that was incompatible with normal growth. This was supported by the fact that neither x-ray films of the wrist nor determinations of serum calcium, phosphorus and alkaline phosphatase values showed changes suggestive of rickets.

Again, relating the calcium intake to the protein intake, or more properly to the nitrogen balance, is pertinent. Bone growth occurs as the result of protein matrix formation. Secondly, calcium salts are deposited in the matrix. Consequently, when skeletal protein anabolism is limited, the amount of calcium that can be deposited is necessarily limited.

Effect of Calories on Nitrogen Balance

The foregoing nutritional studies thus suggested that caloric deficiency was the cause of the retarded growth in certain patients. To investigate further the possible significance of this idea, one of the underweight and apparently calorically undernourished children of Group C was admitted to the Metabolic Ward of the Massachusetts General Hos-

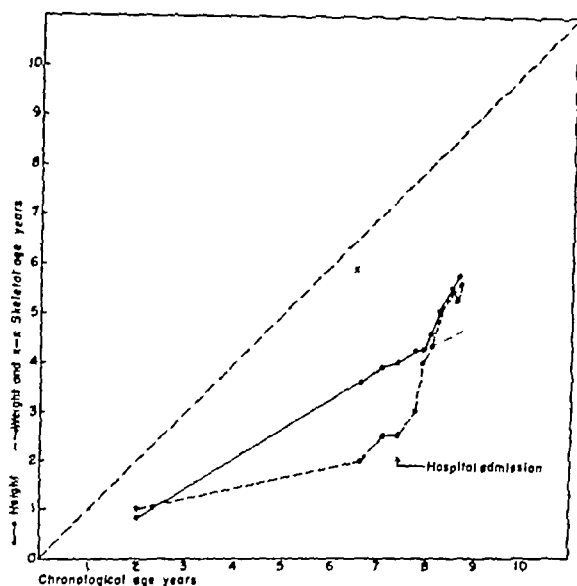


FIGURE 9 Growth in Height and Gain in Weight of Same Patient before and after Hospital Admission When Dietary Intake Was Increased

Results are expressed as height age (black circles connected by solid line) and weight age (white circles connected by interrupted line) plotted according to the scale on the ordinate against chronological age (abscissa). One measurement of skeletal age is represented (X). The diagonal dashed line indicates where the height, weight and skeletal age symbols should fall if the patient were average normal for her age and sex.

pital for a study of the relation of variations in caloric and in protein intake to the growth rate as measured by the nitrogen balance. The techniques used were similar to those reported elsewhere.⁴¹ The appearance of this child at the time of admission is presented in Figure 3A. Figure 8 sets forth the chief metabolic observations. During Period A the patient received a diet calculated to yield approximately 1200 calories and 48 gm of protein a day. On this regime she gained weight at the rate of about 35 gm and retained nitrogen at the rate of about 0.6 gm daily. During Period B the patient received the same protein intake, but the daily content of the diet was reduced to 1000 calories. On this diet the patient lost body weight and showed a less positive nitrogen balance (about 0.4 gm per day). Finally, in Period C the intake was restored

to a level of 1200 calories, but the daily protein intake was reduced to 25 gm, or 1.9 gm per kilogram of body weight. On this diet she gained weight at a rate of 30 gm and stored nitrogen at the increased and rapid rate of 0.7 gm a day. Not shown in the figure are numerous measurements of the basal metabolic rate and of the rate of insensible weight loss. Neither of these measurements gave grossly abnormal values, and neither showed any striking changes during the course of these periods.

These observations suggest that in this child the caloric intake was a more important determinant of the rate of growth (protein anabolism as reflected by the nitrogen balance) than the protein intake. They further confirm the thesis that a daily protein intake of approximately 2 gm per kilogram of body weight is sufficient to permit rapid nitrogen storage, for the anabolism of 0.7 gm of nitrogen per day should yield approximately 7 kg of true muscle in a year.⁴² The other implication of these findings — namely, that this child should grow rapidly in stature if continuously provided with an adequate diet — is borne out by the measurements recorded in Figure 9. It is seen that whereas the patient had grown and gained exceedingly slowly during the years prior to these studies, she gained and grew extremely fast during the succeeding months, in the course of which she ate much more food.

Viewed as a whole, therefore, these clinical, nutritional and metabolic studies coupled with data in the literature¹⁸ suggest that the retarded growth of the thin patients of the present series was due primarily to caloric malnutrition. Because the calories were inadequate, it may be that the body tended to adapt itself by using protein for energy rather than growth. This is discussed below.

Psychiatric and Social Studies

The possibility that some of these children were calorically undernourished led to attempts by the nutritionists and medical staff to improve the diet of thin patients in Groups B and C. These efforts met with little success, often because the children could not be interested in the idea of eating more food. In 4 of 21 cases this lack of interest could be attributed to moderately marked mental deficiency (Fig 10). On the other hand, no explanation was provided by the information obtained in the other 17. Accordingly, these patients were studied from the social-service and psychiatric points of view. For control purposes 7 dwarfed but apparently well nourished patients were likewise studied (Fig 10).

As indicated in the figure, the patients fell into six groups. In Group I nothing remarkable was found. As mentioned above, the children of Group II were found to be moderately mentally deficient as evidenced by an intelligence quotient of about 70. Group III was made up of patients from families whose economic resources were markedly limited and in which the mother's intellectual equipment

was not sufficient to enable her to carry through adequate housekeeping and nutritional management of the child. In Group IV it was found that for emotional reasons the mother was unable to accept and perform her nurturing functions with the child. Some of these mothers had not wanted the pregnancy and had emotionally rejected the child after birth. In others adjustment to womanhood in general and motherhood in particular was poor. In still others poor marital adjustment and hos-

similar studies on run-of-the-mill hospital patients are not yet at hand. The need for such studies is clearly evident. Nevertheless, the available information suggests strongly that the thin dwarfs were undernourished either because of anorexia due to emotional disturbances or mental deficiency or because of a combination of such disturbances and poverty and ignorance on the part of the parents.

Although the period of follow-up study has been too short to warrant any detailed evaluation of

7 WELL NOURISHED DWARFS

21 THIN DWARFS

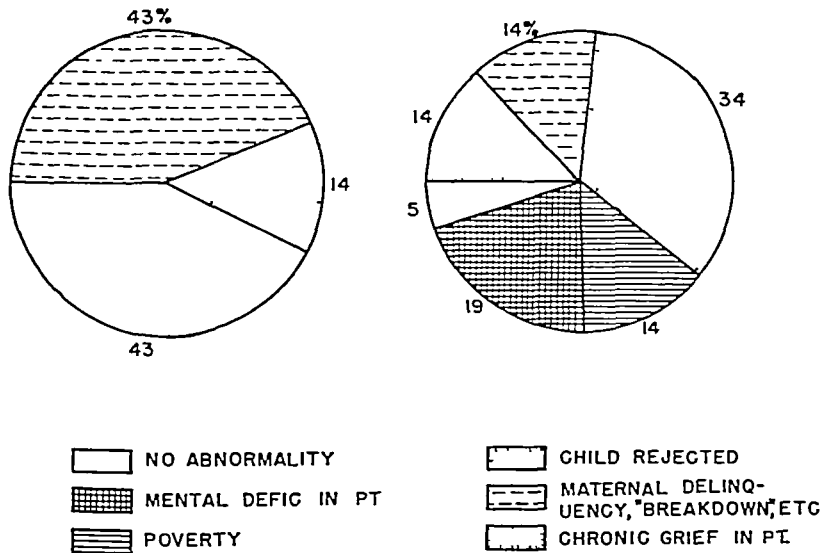


FIGURE 10 Incidence of Mental Deficiency, Poverty and Various Emotional Disturbances in 21 Thin Dwarfs Compared with that in 7 Well Nourished Dwarfs

tility to the husband led to hostile attitudes toward the child. In Group V, because of a "nervous breakdown" or delinquency on the part of the mother, the home situation was as seriously disturbed as in the preceding group. One mother was in jail because of indecent conduct. Another had had a psychotic reaction in the puerperium. The others had reactive depressions making them profoundly preoccupied with their own concerns and inaccessible to the children. The children of Group VI all had severe emotional reactions, with chronic grief* and anorexia due to a broken home brought about by death, divorce or desertion.

It will be noted that the incidence of social or psychiatric difficulties was remarkably high in the thin dwarfs. The control group of apparently well nourished dwarfs was too small to permit any clear analysis. The incidence of difficulties, however, was lower in the control subjects. Unfortunately,

psychiatric therapy, it can be said that such therapy has already been followed by a major improvement in appetite in 3 children of Groups B and C. After the change in appetite these children have shown a decided increase in the rate of weight gain and subsequently in the rates of growth and maturation. The patient presented in Figures 8 and 9 is an example. The prognosis for such successful psychotherapy is probably fair to good in about half the children studied to date.

The Role of Growth Hormone

There is evidence that during the major part of childhood, growth in stature (protoplasmic anabolism) is dependent not only on the assimilation and transportation of building materials (protein, minerals and so forth) to the growing end organs but also on the presence of the pituitary growth hormone.¹² Growth defined as an increase in stature due to the construction of new skeletal (proto-

*This type of reaction has been described elsewhere by one of us (E. L. W.)

plasmic) tissue proceeds exceedingly slowly in the absence of this hormone, even when the dietary intake is more than sufficient to meet the requirements for maintenance and growth. Under these circumstances the protein ingested is catabolized, and any surplus calories are stored as body fat. Contrariwise, provided there is an intake of building materials in excess of minimum maintenance requirements, growth can proceed under the influence of growth hormone even if the total caloric

intake is insufficient to meet the total energy requirements¹². Under such circumstances any caloric deficit is made up by the combustion of body fat. According to these ideas it may be postulated that children such as the present patients in this series, who were ingesting every day 2 gm of protein per kilogram of body weight, should have grown at a satisfactory rate had they been producing appropriate amounts of pituitary growth hormone. In other words, the slow growth of these children may have been due, in the final analysis, to a relative deficiency of pituitary growth hormone. Although it was impossible to test this theory by the administration of a potent preparation of pituitary growth hormone, it was possible to give the substitute pro-

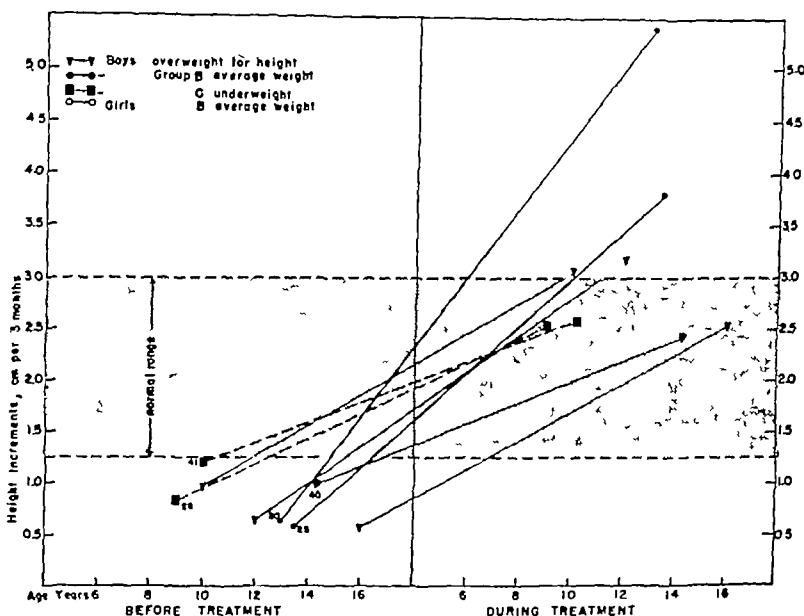


FIGURE 11 Effect of Oral Methyl Testosterone Therapy on Growth Rates of 8 Dwarfed Children

Four of these children were well nourished, and 4 of them were thin. The rates of growth before treatment were observed over a period of at least six months. The rates of growth during treatment indicate the rates found during the first approximately three months after therapy was begun. The position of the symbols for each child relative to the abscissa indicates roughly the age of the patient at the time when therapy was started. The numbers beside the symbols are case numbers. The shaded area depicts the approximate normal limits of growth increments expressed, like the results, as centimeters per three months.

intake is insufficient to meet the total energy requirements¹². Under such circumstances any caloric deficit is made up by the combustion of body fat.

According to these ideas it may be postulated that children such as the present patients in this series, who were ingesting every day 2 gm of protein per kilogram of body weight, should have grown at a satisfactory rate had they been producing appropriate amounts of pituitary growth hormone. In other words, the slow growth of these children may have been due, in the final analysis, to a relative deficiency of pituitary growth hormone. Although it was impossible to test this theory by the administration of a potent preparation of pituitary growth hormone, it was possible to give the substitute pro-

tein anabolic agent — methyl testosterone* — to 4 thin patients of the present series, as well as to 4 similarly dwarfed but well nourished children. Following a control period of several months these patients were given 20 to 30 mg of the drug by mouth daily for a period of about three months. The data in Figure 11 show that all were growing at an abnormally slow rate during the control period. During the period of therapy, on the other hand, there was universally a striking increase in growth rate

to normal or superior levels. These observations indicate that the thin as well as the well nourished dwarfs were capable of normal growth rates. To the best of our knowledge this change in rate was not accompanied by important changes in appetite. The observations may also be interpreted as suggesting again that the ultimate cause of the abnormally slow growth during the control period was a relative deficiency of the naturally produced pituitary growth hormone.

Such a thesis is well supported by the evidence in the literature. It is known that malnutrition secondary to famine or to anorexia nervosa is accompanied by a tendency to amenorrhea, asper-

*Kindly supplied by Schering Corporation, Bloomfield, New Jersey.

matogenesis, retarded sexual maturation and the like.⁴⁴⁻⁴⁷ These changes in all probability signify that the organism tends to adapt itself to nutritional privation by becoming relatively hypopituitary

Recovery from Malnutrition Accompanied by Failure to Resume Normal Growth

These thoughts have a practical bearing on the problem presented by the few dwarfed but relatively heavier and apparently well nourished patients of the present series. The medical and nutritional histories obtained on some of these children suggested strongly that they had undergone a period of nutritional privation in earlier childhood. It is conceivable that such children adapted themselves to the malnutrition by a diminution in pituitary activity but failed to resume normal pituitary function when the diet improved. Patient C in

nourished. Unfortunately, no early records of his weight are available. The first records of height (Fig. 12), however, show that he had grown very little between the ages of six and nine years. At about the eighth year he was adopted into another home, where he promptly gained much weight. Figure 12 shows that although he continued to gain in weight from the ninth to the thirteenth year, he failed to accomplish a corresponding increase in

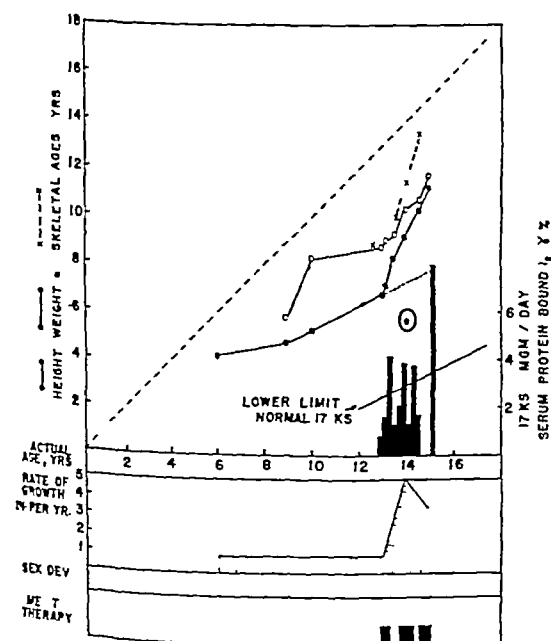


FIGURE 12 Observations on the Growth in Height, Gain in Weight and Skeletal Maturation and 17-Ketosteroid Output of a Dwarfed Boy (Patient C, Fig. 3)

This boy was eventually treated intermittently for a period of two years with 20 to 30 mg of methyl testosterone daily by mouth. The form of this chart is similar to that of Figure 10

Figure 3, as well as Figures 12 and 13, illustrates this possibility

This patient was said to have been normal up to the age of four years. At that time his mother died, with the result that for approximately four years he had to shift for himself in the daytime while his father was away at work. During this period he is reported to have subsisted largely on coffee and doughnuts. When eight years of age he was found by a relative to be small and poorly

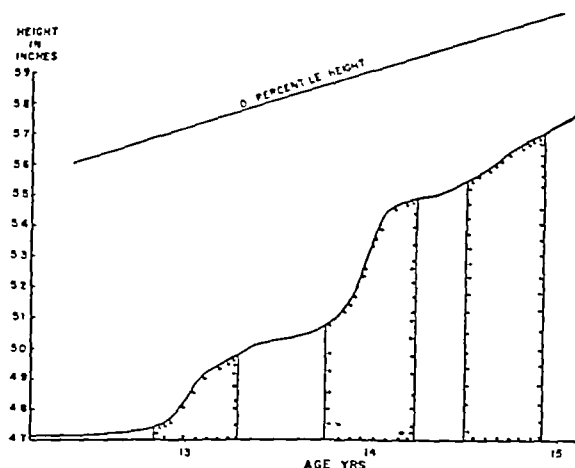


FIGURE 13 Detailed Record of Increments in Height of Same Patient before, during (speckled areas) and After Periods of Methyl Testosterone Treatment

stature. Physical examination at the age of thirteen years revealed an apparently healthy, intelligent and well nourished, but abnormally small boy. There were no evidences of sex maturation. Ordinary clinical laboratory tests, as well as roentgenograms of the skull, disclosed nothing of note. The bone age was retarded four years. The urinary 17-ketosteroid output was likewise below normal limits.

In view of the fact that the nutrition seemed to be adequate, no attempt was made to stimulate growth by dietary therapy. Since the dwarfism, together with the retarded skeletal maturation and lowered urinary ketosteroid values, suggested a lack of normal pituitary activity, the patient was treated intermittently with the substitute growth hormone, methyl testosterone, over a period of two years. This was given by mouth in daily doses of between 20 and 30 mg. Figure 12 reveals that this therapy promptly induced a marked acceleration in growth rate. There was a corresponding increase in the rates of weight gain and skeletal maturation. The urinary 17-ketosteroid output also tended to rise from abnormally low to normal levels during periods of methyl testosterone therapy. Figure 13 gives more detailed information and shows again that prior to this medication, the growth rate was exceedingly slow. During the first period on methyl testos-

terone, the rate of growth increased markedly, but returned to essentially pretreatment levels when the drug was discontinued. This deceleration of growth indicated that the first growth spurt was not spontaneous. A similar response occurred during the second course of therapy, but this time there was no decline in growth rate when the drug was stopped. The administration of the drug for the third and final time had no appreciable effect on the rate of growth. From this time on the patient continued to show satisfactory progress in growth, weight gain, skeletal and sexual maturation and urinary ketosteroid excretion. These observations suggest strongly that he had in fact been suffering from a functional type of hypopituitarism and that during the therapy he resumed normal pituitary function.

A similar progress in growth was noted in 4 other patients of Group B following one or two courses of methyl testosterone of three months' duration. It is tempting to postulate, therefore, that testosterone not only directly stimulates protoplasmic anabolism but also promotes increased pituitary activity. This contention is supported by the changes in urinary 17-ketosteroid output observed in the patient described above. Methyl testosterone is not per se metabolized and excreted as a urinary 17-ketosteroid.⁴⁸ Therefore, the increase in ketosteroid output noted during periods of methyl testosterone therapy presumably reflects an increase in the rate of production of 17-ketosteroid precursors by the glands that normally produce them — namely, the adrenal cortices or testes, or both. Since the activities of the glands are controlled by the anterior portion of the pituitary body, the rise in ketosteroid output appears to signify that an increase in pituitary activity had taken place. It is entirely possible that a similar increase in pituitary activity would have occurred spontaneously at a later date.

Mention should probably be made of the alternative possibility that malnutrition or emotional disturbances, or both, induced an overproduction of anti-growth hormones by the adrenal cortex — the "S" hormone of Albright.³⁰ This seems relatively unlikely. Consideration of other explanations for the retarded growth of the patients seems inappropriate at present. The purposes of this paper will have been fulfilled if the problems presented by physically normal, dwarfed children gain wider attention.

SUMMARY

A sizable number of physically sound but abnormally small children were investigated. It was noted that some were grossly underweight for their height and that the great majority appeared to have scanty subcutaneous fat stores. Nutritional studies revealed that although the intake of building materials such as protein was probably adequate for growth, the total caloric intake appeared to be undesirably low. In the majority of cases this pre-

dominantly caloric malnutrition appeared to be related to anorexia—secondary to emotional disturbances. In 3 cases correction of emotional difficulties resulted in an improvement in appetite that was followed, in turn, by a rapid gain in weight and an appreciable increase in the rates of growth and maturation.

A few children failed to resume normal growth when the dietary inadequacies had been corrected. Furthermore, it was found that the growth rate of both poorly nourished and well nourished dwarfs could be increased markedly by the administration of a protein anabolic or growth hormone — namely, methyl testosterone — without any evident change in diet. In a few well nourished dwarfs growth continued spontaneously at a satisfactory rate after one or two short courses of testosterone therapy. These observations coupled with the evidence of the literature concerning the value of anabolic hormones and especially of the pituitary growth hormone as determinants of growth rate during childhood⁴⁹ suggested that the dwarfism in this group of children was due to a functional hypopituitarism occasioned by the limited caloric intake. If this thesis is correct, it may be assumed that this hypopituitarism reflected a homeostatic or adaptive reaction to the malnutrition.

The use of testosterone as initial treatment for the stunted growth of nutritional dwarfs seems illogical, correction of emotional and nutritional inadequacies commands first attention. On the other hand, when correction of these factors fails to accelerate growth and when the possibility of hypothyroidism has been ruled out, the daily oral administration of about 20 mg of methyl testosterone for one or two short periods may, especially in retarded boys of adolescent age, be followed by an acceleration in spontaneous growth and maturation processes. It cannot yet be said that such hormonal therapy is free from permanently harmful effects on testicular function.

REFERENCES

1. Cushing, H. W. *The Pituitary Body and Its Disorders*. Clinical states produced by disorders of the hypophysis cerebri. 341 pp. Philadelphia: J. B. Lippincott & Co., 1912.
2. *Idem*. Acromegaly from surgical standpoint. *Brit M J* 21 and 48-54, 1927.
3. *Idem*. "Dispituitarism" twenty years later, with special consideration of pituitary adenomas. *Arch Int Med* 51:487-557, 1933.
4. Shelton E. K., Cavanaugh L. A. and Evans H. M. Hypophyseal infantilism: treatment with anterior hypophyseal extract: preliminary study. *Am J Dis Child* 47:719-736, 1934.
5. Buchanan, J. A., and Ballweg, H. A. Case of pituitary dwarfism treated with antuitrin-G. *Endocrinology* 24:565-571, 1939.
6. Buxton, St. J. D. Pituitary cyst with dwarfism and delayed union of fracture. *Brit J Surg* 27:181-183, 1939.
7. Bronstein, I. P., and Fabricant, N. D. Pituitary dwarfism with atrophic rhinitis. *Am J Dis Child* 60:1140-1146, 1940.
8. Gjörup, E. Hypophyseal nanism resulting from craniopharyngioma. *Acta paediat* 27:503-516, 1940.
9. Fraser, R. W., Forbes, A. P., Albright, F., Sulikowitch, H., and Reidenstein, E. C. Jr. Colorimetric assay of 17 ketosteroids in urine: survey of use of this test in endocrine investigation, diagnosis and therapy. *J Clin Endocrinol* 1:234-256, 1941.
10. Farber, J. E., Goldstein, K., and Beasick, W. F. Simmonds disease with craniopharyngioma. *J Clin Endocrinol* 1:688-690, 1941.
11. Talbot, F. B., and Talbot, N. B. Pituitary and suprarenal glands: gonads: pineal body: sex precocity, obesity and progeria. Chapter 40 in *Brennemann's Practice of Pediatrics*. Hagerstown: W. F. Prior Co., Inc. 1944. Pp. 1-41.

12. Talbot, N. B., and Sobel, E. H. *Endocrine and Other Factors Determining the Growth of Children*. Vol. 2. *Advances in Pediatrics*. New York: Interscience Publishers (in press).
13. Kennedy, C. M., and Lister, W. A. Case of suprarenal hypernephroma. *Lancet* 2:749-751 1927.
14. Lefebvre, G. Syndrome de Cushing datant de trois ans chez une fillette de douze ans: détails cliniques, discussions thérapeutiques. *Bull Soc pédiat de Paris* 37: 326-333 1939.
15. Marks, T. M., Thomas, J. M., and Warkany, J. Adrenocortical obesity in children. *Am J Dis Child* 60:923-942 1940.
16. Engelbach, W. Growth hormone: report of case of juvenile hypopituitarism treated with Evans' growth hormone. *Endocrinology* 16: 1-19 1932.
17. Engelbach, W., Schaefer, R. L., and Brosius, W. L. Endocrine growth disorders: diagnosis and treatment. *Endocrinology* 17:250-262 1933.
18. Wang, C. C., Hodgen, C., Kaucher, M., and Wing, M. Metabolic study of case of Lorain type of infantilism. *J Biol Chem* 100: 701-713 1933.
19. Goldberg, M. M. Treatment of pituitary infantilism with antuitrin: report of case. *Endocrinology* 18:233 1934.
20. Idem. Treatment of pituitary infantilism with anterior pituitary extract. *Endocrinology* 20:854 1936.
21. Taylor, N. M. Pituitary dwarfism: treatment with growth hormone. *Endocrinology* 22:707-715 1938.
22. Lawrence, C. H., and Harrison, A. Pituitary dwarfism: case report illustrating response to treatment. *Endocrinology* 23:360-363 1938.
23. Looney, J. M. Treatment of pituitary dwarfism with growth hormone. *Endocrinology* 26:163-166 1940.
24. Schaefer, R. L., and Strickroot, F. L. Endocrine dwarfism. *Endocrinology* 26:599-604 1940.
25. Greene, J. A., and Johnston, G. W. Metabolic changes by extracts of anterior hypophysis in primary pituitary and in nonpituitary dwarfs. *J Clin Endocrinol* 1:327-330 1941.
26. Jackson, R. L., and Kelly, H. G. Growth charts for use in pediatric practice. *J Pediatr* 27:215-229 1945.
27. Jamin, F. Die hypophysäre Plethora (Cushingsche Krankheit: pituitary basophilism). *Münchener med Wochenschr* 81:1045-1048 1934.
28. Freyberg, R. H., Barker, P. S., Newburgh, L. H., and Collier, F. A. Pituitary basophilism (Cushing's syndrome): report of verified case with discussion of differential diagnosis and treatment. *Arch Int Med* 58:187-212 1936.
29. Gross, R. E. Neoplasms producing endocrine disturbances in child hood. *Am J Dis Child* 59:579-628 1940.
30. Albright, F. Cushing's syndrome: its pathological physiology, its relationship to adreno-genital syndrome and its connection with problem of reaction of body to injurious agents (also a reaction of Selye). *The Harvey Lectures* 38:123-186 1942-43.
31. Talbot, N. B. Measurement of obesity by creatinine coefficient. *Am J Dis Child* 55:42-50 1938.
32. Stuart, H. C., and Sobel, E. H. Thickness of the subcutaneous tissue by age and sex in childhood. *J Pediatr* 28:637-647 1946.
33. Burke, B. S., and Stuart, H. C. Method of diet analysis: application in research and pediatric practice. *J Pediatr* 12:493-503 1938.
34. Beal, V. A., Burke, B. S., and Stuart, H. C. Nutrition studies on children living at home. I. Calory intakes on basis of age from one through ten years. *Am J Dis Child* 70:214-219 1945.
35. National Research Council. *Recommended Dietary Allowances*. Reprint and Circular Series No. 122, August, 1945. Revised 1945. Washington, D. C.
36. Holt, L. E., and Fales, H. L. Food requirements of children. I. Total caloric requirements. *Am J Dis Child* 21:1-28 1921.
37. Bartlett, W. M. Protein requirement as determined in diabetic children. *Am J Dis Child* 32:641-654 1926.
38. Roberts, L. J. Scientific basis for recommended dietary allowances. *New York State J Med* 44:59-66 1944.
39. Shohl, A. T. *Mineral Metabolism*. 384 pp. New York: Reinhold Publishing Co. 1939.
40. Mitchell, H. H. Adaptation to undernutrition. *J Am Diet A* 20:511-515 1944.
41. Talbot, N. B., Butler, A. M., Pratt, E. L., MacLachlan, E. A., and Tannheimer, J. Progenia: clinical, metabolic and pathologic studies on patient. *Am J Dis Child* 69:267-279 1945.
42. Talbot, N. B., Butler, A. M., and MacLachlan, E. A. Effect of testosterone and allied compounds on mineral, nitrogen and carbohydrate metabolism of girl with Addison's disease. *J Clin Investigation* 22:589-599 1943.
43. Lindemann, E. Symptomatology and management of acute grief. *Am J Psychiat* 101:141-148 1944.
44. Mason, K. E., and Wolfe, J. M. Physiological activity of hypophysis of rats under various experimental conditions. *Arch Rec* 45:232 1930.
45. Werner, S. C. Failure of gonadotropic function of rat hypophysis during chronic inanition. *Proc Soc Exper Biol & Med* 41:101-109 1939.
46. Mahnos, M. G., Pomeantz, L., Smelser, J., and Kurzrok, R. Estrus inhibiting effects of inanition. *Proc Soc Exper Biol & Med* 40:79-83 1939.
47. Klinefelter, H. F., Jr., Albright, F., and Griswold, G. C. Experience with quantitative test for normal or decreased amounts of follicle stimulating hormone in urine in endocrinological diagnosis. *J Clin Endocrinol* 3:529-544 1943.
48. Reifenshtein, E. C., Jr., Forbes, A. P., Albright, F., Donaldson, E., and Carroll, E. Effect of methyl testosterone on urinary 17-ketosteroids of adrenal origin. *J Clin Investigation* 24:416-434 1945.

A CLINICAL SYNDROME SIMULATING POLIOMYELITIS

RICHARD H. YOUNG, M.D.*

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DURING the week August 11 to 18, 1946, a total of 34 new cases of poliomyelitis were reported in Nebraska, 176 cases having been reported for that year. With serious epidemics in the neighboring States of Minnesota, South Dakota and Colorado, there was considerable apprehension on the part of the people of this area. On the front page each day the press reported the new cases and the precautions to be taken. In letters to editors, readers asked for a spraying of the City with DDT, and offered new epidemiologic theories. The terror that past generations manifested toward "the plague" was displayed toward poliomyelitis. Precautions dictated by fears were at times extreme, particularly in this year, when transmission by contact and carriers had been stressed. In this situation of social anxiety, it was not remarkable that evidence of neurotic behavior was found.

During the week when 34 new cases of poliomyelitis appeared in the State, 5 cases closely simulating poliomyelitis were observed in private practice, in 4 of which the patients had hysterical paralysis of one or more extremities. These cases are presented below because of a similarity in the situational and psychologic mechanisms involved.

It is believed that an elucidation of the clinical features of these cases may serve to accent the importance of anxiety and other emotional factors in suspected cases of poliomyelitis. These cases also illustrate the value of determining the nature of the paralysis, for purposes of diagnosis as well as for treatment.

CASE REPORTS

CASE 1 L B, a 25-year-old housewife, was referred because of the development of a headache, chiefly occipital, stiffness of the neck and weakness in the left arm.

A nephew who had been living with the patient's family on a farm had developed poliomyelitis 5 days previously and had been sent to Lincoln, Nebraska, for hospital treatment. This experience had been disturbing to the patient and to the neighbors of the surrounding countryside, one of whom, in declining to pay her a visit, stated that she would be glad to come to the patient's home after the first frost.

Examination revealed the cranial nerves to be normal, except for some difficulty in moving the head from side to side, which was attributed to muscle stiffness. There was no particular stiffness in flexion of the head on the neck. The motor status showed the left arm to be held in a position of flexion and to be weak and limited in movements, but increased in muscle tone. The left leg also showed a minor degree of diffusely distributed weakness. The deep reflexes were equal and active. Superficial reflexes were present and normal in type. Sensory status revealed a left hemihypalgesia.

At the time of admission the patient had a temperature of 99.4°F and after the examination the nature of her illness had been explained to her, she was considerably relieved. She

was given 0.4 gm of sodium amytal (6 gr) that night, and on the next morning, with encouragement, she showed a full range of motor power and was allowed to return home.

CASE 2 G H, a 33-year-old housewife, was seen as an outpatient at the Lutheran Hospital because of backache and weakness of the left leg. Her physician reported a temperature of 99.6°F.

The patient stated that in 1939 her daughter had developed poliomyelitis, which had seemed to appear suddenly, the first awareness of the disease being when she fell out of a chair during an illness that had been considered to be influenza. For the previous day the patient had complained of backache and weakness in the left leg. In spite of her ability to walk from the car to the hospital, she was confident that she had poliomyelitis.

Neurologic examination revealed the cranial nerves to be normal. Motor status showed a questionable diffuse type of weakness in the left leg. The deep reflexes were equal and active. Superficial reflexes were present, without any abnormal forms. Sensory status was normal.

The patient, who was reassured that she did not have poliomyelitis, was obviously relieved emotionally and left the hospital secure and symptom free.

CASE 3 E B, a 23-year-old housewife, was seen at the hospital because of the loss of motor power in both legs, particularly the left.

Ten days prior to admission the patient had experienced an upper respiratory infection, from which she had appeared to recover. On the day before admission, she had gone to a celebration in a neighboring town and had returned that evening extremely tired. Shortly after going to bed, she became concerned because she was unable to move the left leg, and later noticed weakness in the right. The past history revealed that at the age of 12 she had had an episode of weakness in both legs, and during the course of her life there had been many manifestations of neurotic behavior.

On admission the temperature was 97.4°F. The patient did not seem to be under any particular tension and was quite composed. Neurologic examination showed the cranial nerves to be normal. Motor status revealed normal motor power in the upper extremities, but in both legs there was a weakness associated with increased muscle tone, more marked on the left side. There was limitation in movement, flexion and extension of the toes. The deep reflexes were bilaterally exaggerated. The superficial reflexes were normal in type, without pathologic manifestations. There was a bizarre type of sensory loss in the lower extremities that did not conform to any peripheral or segmental pattern.

The patient was assured that she did not have poliomyelitis, but when the nature of her illness was explained, she found the explanation impossible to accept on a functional basis. Behind the conversion features were personal and emotional problems of which this patient had little, if any, conscious appreciation. She was discharged on the day of admission.

CASE 4 R S, a 24-year-old carpenter, was admitted to the hospital because of headache, stiffness in the neck and backache.

This patient had been exposed to a sister-in-law who had developed poliomyelitis about 3 weeks previously, and he came to the hospital greatly disturbed, the complaints mentioned above having developed on the preceding day.

Physical examination revealed a temperature of 98.8°F. The patient and his wife were obviously panicky and quite sure that the patient had poliomyelitis. Neurologic examination was entirely negative, except for some questionable stiffness in the neck. A lumbar puncture showed a normal spinal-fluid pressure, with 1 cell per cubic millimeter.

The patient was reassured that he did not have poliomyelitis, and the nature of the illness was explained to him. He was discharged on the day following admission.

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CASE 5 C. C., a 30-year-old housewife, was seen at the Douglas County Hospital because of inability to move the arms or legs.

The history disclosed that for several days the patient had been constipated and that on the morning of admission, while straining at stool, she passed a considerable amount of blood, which she described as making her feel weak and frightened. She lay down and was discovered to be feverish, and shortly thereafter called on a physician at his office. Because of the fever and muscle weakness, she was advised to report to the isolation ward. The past history was of significance, in that the patient had always been nervous and had just returned from a 3 weeks' stay at a hospital, where she had been treated for "nerves."

Physical examination revealed a temperature of 103°F, with redness of the throat. The patient appeared tense and apprehensive, expressing the hope that her children would not contract her illness. Neurologic examination showed the cranial nerves to be normal. There was a diffuse type of weakness of all four extremities that was slightly more marked in degree peripherally. The muscle tone was slightly increased. The deep reflexes of the arm were present and equal. The knee jerks were questionably present, and the left ankle jerk could not be definitely obtained. There was a bizarre type of hypalgesia in all four extremities that failed to follow any peripheral or segmental distribution. The sensory loss was more marked on the right side than on the left. Lumbar puncture showed a normal spinal-fluid pressure and 6 cells per cubic millimeter, without elevation in the protein.

It was explained to the patient that she had an upper respiratory infection, but not poliomyelitis, and the nature of the muscle weakness was described. With encouragement, she rapidly regained motor power and was discharged from the hospital after the pharyngitis had subsided.

DISCUSSION

A review of these cases reveals certain interesting correlations. Three patients had relatives who had developed poliomyelitis, 2 in the recent epidemic. Four had an elevation of temperature on admission, and all complained of pain either in the back or in the neck. In the 4 patients who showed weakness of one or more extremities, the weakness was associated with an increase rather than a decrease of muscle tone and with intact or exaggerated reflexes in all but 1. In 3 cases there were subjective or objective paresthesias. The recovery of motor power in all 4 cases was prompt following reassurance and an explanation of the nature of the illness.

A composite picture of the reported cases might be reconstructed as follows: a social attitude of marked anxiety precipitated by the development of poliomyelitis in the community, a marked intensifi-

cation of anxiety by the appearance of poliomyelitis in the family group, the development of concern about exposure, subsequent development of an upper respiratory infection, with attendant symptoms, as well as the somatic expressions of anxiety in the form of neck stiffness, tightness in the throat, feelings of suffocation and weakness; and finally a localization of the weakness in one or more extremities as a conversion symptom, with a prompt return of function on reassurance and explanation.

In the treatment of this group of cases, certain preventive measures deserve consideration. First of all, a factual presentation of poliomyelitis by the press is indicated. If a daily report is to be made, it might best be presented in an accessible part of the paper other than the front page, unless some emergency exists. A special effort should be made to appease any unreasonable fears of members in a family in which a case of poliomyelitis has developed. When the syndrome described above develops with hysterical paralysis or other neurotic features simulating a poliomyelitis, reassurance effects a prompt symptomatic cure. The response to reassurance and explanation in the cases in which there was marked fear because of association or exposure to patients with the disease suggests that the motor loss had as its basis an overwhelming fear, which caused a dissociation in motor activity. It is as though the patient had become "paralyzed with fear." The more usual conversion mechanism found in hysterical paralyses seemed to be responsible in Case 3. The depth of psychotherapy needed depends on the dynamics of the individual case.

SUMMARY

Attention is called to the existing social attitudes toward poliomyelitis and to individual reactions to this anxiety-provoking situation.

Five cases of suspected poliomyelitis are reported that had many features in common, 4 patients presenting hysterical paralysis of one or more extremities. The course in these cases is described.

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The patient was reassured that he did not have poliomyelitis, and the nature of the illness was explained to him. He was discharged on the day following admission.

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dermatitis following the injection of 100,000 units of penicillin, no tests were done. Strickland³⁰ observed a patient who developed during a second course of penicillin treatment an immediate severe generalized urticaria and angioneurotic edema. No skin tests were performed. Binkley¹³ reported a case of dermatitis of the face with a negative intradermal test. When this patient was injected with 60,000 units intramuscularly, a papular dermatitis of the face, hands and feet followed and persisted for seven days. Flinn²¹ described a patient who suffered a severe urticarial reaction from injections of one brand of penicillin, although clinically and by skin tests he was not allergic to one of the other brands. One of Goldman's²⁷ cases developed vesicular dermatitis from parenteral penicillin and exhibited an urticarial skin test reaction, a tuberculin type of reaction and a positive patch test. A case of clinical contact dermatitis observed by Truitt²² demonstrated positive intradermal and patch tests followed in nine months by a tuberculin type of reaction. Graves²³ reported an acute vesicular reaction that began after the first injection of penicillin for a low-grade prostatitis and was followed by a superficial form of desquamation. This patient gave a positive intradermal test to 500 units of penicillin and to a 1:100 dilution of trichophyton. In a similar case the patient gave a negative intradermal reaction to penicillin and a positive reaction to the trichophyton extract. It was not decided whether the lesions were a manifestation of sensitivity to penicillin or some impurity in the penicillin solution used or were due to the too rapid liberation of toxic products from some unsuspected fungous or bacterial focus or to an alteration of local immunity that allowed dormant fungous spores to become active. In 3 of Goldman's²⁷ cases, with histories of recurrent mycotic dermatitis of the hands or feet, penicillin provoked a pompholyx-like dermatitis. It is interesting that of 17 patients with previous fungous disease observed by Cormia³ 88 per cent showed an immediate reaction to intradermal tests with penicillin, although none had been treated previously with penicillin. Lamb³⁴ reported a case of syphilis under treatment with penicillin in which the patient developed a vesicular eruption of the fingers, penis and crural areas and gave a positive wheal-reaction intradermal test to penicillin. Another patient who during the course of penicillin injections for actinomycosis developed a vesicular eruption of the crural region, scrotum and webs of the fingers presented a negative intradermal test to penicillin and trichophyton but a positive intradermal test to oidiomycin. In 10 cases of skin eruptions treated by penicillin, Heinlein³⁵ found that the drug caused a marked aggravation of the existing skin eruptions, frequently associated with the appearance at other sites of new similar cutaneous manifestations accompanied by systemic reactions. This phenomenon was considered a manifestation of

an underlying bacterial allergy. Price³⁶ reported a case of reaction to penicillin consisting of purpuric eruptions with subsequent wheals and arthralgia in which the patient gave a positive reaction to intracutaneous injections of serum with penicillin. Scratch and patch tests with penicillin solution were negative. Sullens³⁷ presented a case exhibiting urticaria, arthralgia and generalized lymphadenopathy that began six days after a second course of penicillin had been instituted; this patient presented a negative skin test to the penicillin solution, but the skin testing caused the appearance of urticarial lesions of the upper arm above the area of the test. Binkley's¹³ case of dermatitis from penicillin presented no epidermal or intradermal sensitivity by cutaneous testing, but the patient had a papular edematous eruption of the hands and feet after a test intramuscular injection of penicillin.

Rostenberg^{38, 39} found that 5.5 per cent of 144 subjects gave a tuberculin type of sensitivity reaction to penicillin although they had had no previous contact with the drug. This spontaneous sensitivity seemed to have no eczematous or wheal component. He also reported that properly spaced intradermal injections of penicillin could cause a tuberculin type of sensitivity to develop, during sensitization such patients may develop urticarial reactions. It was not possible to demonstrate a passive transfer of the sensitivity exhibited by persons who showed a tuberculin type of reaction on first contact with penicillin. Epstein¹¹ reported a case of delayed tuberculin-type, infiltrated, itching reaction to both commercial and crystalline penicillin in a nurse who presented a clinical picture of contact sensitivity. All patch tests were negative except when the solution was applied to a site that had previously shown the eruption. Truitt²² observed a case of clinical contact dermatitis with at first a positive immediate intradermal test but nine months later a positive tuberculin type of reaction. Clayton⁴⁰ presented a series of cases of presumed penicillin urticaria in which he was unable to obtain any positive penicillin tests. Likewise, 4 of 56 patients receiving injections of penicillin who developed allergic reactions resembling serum sickness were reported by Haswell⁹ as giving negative patch, scratch and intradermal tests.

CASE REPORT

A 52-year-old man, who had been hospitalized for 20 years with the diagnosis of dementia praecox, was admitted to the infirmary because of a cough and a fever of a few hours' duration.

Previous to the acute onset of these symptoms he had been free of any complaints, working about the hospital grounds every day. The family and personal histories were negative for asthma, hay fever, hives, eczema, angioneurotic edema or other symptoms suggestive of allergy. The record revealed that a dental check had just been completed, with negative x-ray studies for apical abscess or other dental infection. The patient had not been away from the hospital for months, and there was no contagious disease among his known contacts. There was no history of previous administration of penicillin.

ALLERGIC REACTION TO PENICILLIN

Report of a Case

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EXTRACTS prepared from various species of the dermatophytes show potent antigenic properties. Jadassohn,¹ using the Schultz-Dale technic, proved that pathogenic fungi contained not only species-specific antigens but also an antigenic fraction common to all species. Clinically, dermatologists have long been cognizant of explosive reactions from fungus toxins, manifested by generalized "ids" and by bullous eruptions. Therefore, it seemed probable that patients being treated with penicillin would exhibit allergic reactions, either to a common hyphomycetic allergin or to a specific penicillin allergin.

Reactions to penicillin are clinically infrequent, but do occur. A recent case focused attention on this subject and prompted a brief survey of the literature. Florey and Florey² encountered no reactions in 187 patients. In the 500 cases reported by the National Research Council,³ urticaria was observed in 28 per cent, whereas in 209 cases reported by Lyons⁴ the incidence was 57 per cent. Tests by Lyons for cutaneous and ophthalmic sensitivity during and after the reactive phase were negative, and precipitins were absent. Among the 182 patients of Stokes,⁵ skin eruptions appeared in 0.8 per cent. Fifty-nine per cent of the 1418 syphilitic patients treated by Moore⁶ exhibited Herxheimer reactions with fever and usually exacerbation of secondary skin lesions, and allergic eruptions appeared in 1 per cent. Dawson and Hobby⁷ found skin reactions in 3 of 100 cases. Cormia⁸ reported that of 2000 soldiers receiving prolonged penicillin treatment, 6 developed urticaria, 3 a serum-sickness syndrome, 2 erythematovesicular eruptions, 1 erythema nodosum, and 5 transient miliaria; skin tests were positive in 57 per cent of 116 persons tested. The development of symptoms of a low-grade fever, malaise, urticaria and transient edemas was noted by Haswell⁹ in 4 of 56 patients receiving parenteral penicillin. Herrell¹⁰ observed cutaneous sensitivity to skin tests in only 2 of 150 cases of clinical penicillin reactions.

The skin of many persons is known to be sensitive to various molds and mold products. Many cases of clinical contact dermatitis have been reported in the literature. Some of these may have been due to an underlying generalized, tuberculin type of sensitivity, such as that seen in the vesicular dermatophytids of the hands in patients with dermatophy-

tosis of the feet. According to Epstein,¹¹ involvement of the epithelium does not necessarily make an eruption a true eczematous contact dermatitis, and not all dermatitis that is brought about by external contact is immunologically of the contact type. Pyle and Rattner¹² reported a case of dermatitis venenata of the face and genitalia in a pharmacy officer who reacted strongly with a patch test of crystalline penicillin. A similar case was presented by Binkley,¹³ with a positive intradermal and patch test to the penicillin used. Satulsky,¹⁴ Markson¹⁵ and Bedford¹⁶ reported cases of dermatitis of the eyelids with positive patch tests. Silvers¹⁷ performed patch tests on a chemist with penicillin dermatitis of the eyelids and penis and found the test with commercial sodium penicillin positive, and that with crystalline sodium penicillin negative. Benkwith¹⁸ and Schultz¹⁹ observed allergic dermatitis of the eyelids from penicillin instillations, with positive intradermal and patch tests. Barker²⁰ reported the case of a medical officer who developed an acute dermatitis of the face while handling penicillin in laboratory and who exhibited a positive patch test to the penicillin solution but not after the solution had been autoclaved. Michie²¹ described an eczematous reaction to penicillin involving not only the ear being treated but also an almost healed leg wound to which penicillin powder had been applied. This patient exhibited a positive patch test. Vickers²² demonstrated by a case report that penicillin powder can cause a dermatitis when sprinkled on local abrasions; his patient also had a positive patch test. Kleinfeld,²³ Phillips²⁴ and Kern²⁵ reported allergic involvement of the palate and the pharynx in cases in which penicillin was administered orally; no patch tests were reported. Selinger²⁶ observed a dermatitis of the eyelids from penicillin eye drops, but the patch test was negative. Thirteen of 350 cases of various types of cutaneous lesions treated by Goldman²⁷ with penicillin ointment developed clinical contact dermatitis, 11 presenting positive patch tests.

In 1944 Crippe²⁸ reported a case of massive urticaria after the injection of 200,000 units of penicillin in a patient who exhibited a positive intradermal test to the penicillin but a negative intradermal test to the spores. Barker²⁰ presented another case of massive urticarial reaction after the injection of penicillin, with a positive intradermal test to the penicillin solution. Tests with autoclaved solutions were negative. Morris²⁹ reported a case of bullous

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MEDICAL PROGRESS

PHYSICAL MEDICINE

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DURING the war rapid developments occurred in the field of physical medicine. Activities included in this specialty have expanded to comprise more active and diversified treatment during convalescent stages of disease to ensure a speedy return of injured soldiers to combat or workmen to industry. In addition to widening, the field is also reaching greater depths through the establishment of research programs to investigate some of the fundamental problems of the effects of physical agents. Along with these advances it has become apparent that it is necessary for men to receive special training in physical medicine to understand properly the many different types of treatment to be prescribed and to direct adequately technicians, such as physical and occupational therapists and others working in rehabilitation. Special training is also necessary to aid in the proper integration of fundamental and clinical research in this field. Physical medicine can accordingly be said to have emerged as a distinct specialty, although the exact boundaries are still somewhat undefined. The need for specialists has far exceeded the supply. Only a few years ago less than fifty physicians in the country considered themselves as specialists, whereas at present approximately one hundred and fifty men are needed in the Veterans Administration and Army alone.

There has been considerable confusion in the use of terms designating workers in this field. At the time of World War I physiotherapy was the most familiar word, the technicians being known as physiotherapists. Later, the term physical therapy was more generally used, the doctor being designated as a physical-therapy physician, as distinguished from the physical-therapy technician. As the field broadened to include other types of treatment, such as occupational therapy and physical reconditioning, the technicians became known as physical therapists and occupational therapists, and the physician had no single term to indicate his specialty. The American Congress of Physical Medicine, the Society of Physical Medicine and the Council on Physical Medicine of the American Medical Association gave considerable thought to the coming of a suitable term to describe the specialist in physical medicine. The result of this is the word "physiatrist," which has now been quite generally accepted by those in the field of physical medicine but is still unfamiliar to the majority of

physicians and laymen. This term is derived from the two Greek words "physis," meaning physical or natural, and "iatria," meaning treatment.¹

The need for a great many more physiatrists is easily understandable when one considers that they are responsible for the medical direction of rehabilitation programs in the Army, Navy and Veterans Administration, as well as of civilian hospitals, community rehabilitation centers and many industrial medical clinics. This development of industrial rehabilitation, which is one of the most important aspects of physical medicine, is discussed in greater detail below.

The need for fundamental and clinical research has been recognized by many physicians, and the present status has been summarized in a previous paper of this series.² The report of the Baruch Committee on Physical Medicine emphasized the necessity of encouraging such research, and funds have been made available to aid scientists in this field. The work in the various centers devoted to research in physical medicine is still in its infancy but a few preliminary studies reported at the American Congress of Physical Medicine in September, 1946, are of interest.

There have been relatively few new developments in therapeutic technics in the past few years. Because of the interest in physical fitness in wartime, exercise therapy has received the attention of physiologists, psychiatrists and physical educationists, as well as that of the physiatrists. The results of some of their studies are reported below in the final section of this paper.

MILITARY REHABILITATION

Because of the acute manpower shortage occasioned by the war, the problem of returning injured workmen and service men to their former activities was attacked earlier in England than in this country. Since methods now being employed in this country are to a large extent adapted from those in use in England, it may be well to review briefly a recent paper by O'Malley³ describing rehabilitation in the Royal Air Force. There is considerable misunderstanding about the meaning of rehabilitation, but this author states "It denotes the restoration of the injured man to perform his duties — mentally, physically, socially, and technically — as efficiently as he did before he was injured. If we fail to make him equivalent, then he has to be resettled in another trade."

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Physical examination revealed a well developed man who was only moderately ill. The conjunctivas were slightly injected, the scleras were clear, and the pupils were round and regular and reacted to light and to distance. The ears were free of drainage, and the drums normal. The nasal passages were free of discharge, and the oropharynx showed no evidence of infection. There was no cervical adenopathy. Both lungs were resonant, there were a few rales, with an increase in bronchial quality to the breath sounds in the right axillary region. There was no demonstrable enlargement of the heart, the cardiac rhythm was regular, and there were no murmurs. Examination of the abdomen, skin and neuromuscular system was negative. The temperature was 104°F, and the respirations 24.

Examination of the chest showed a pneumonic lesion of homogenous density in the region of the right middle lobe that was diagnosed as lobar pneumonia. The remainder of the lung field was clear. Repeated throat smears and cultures revealed no pathologic organisms.

Examination of the blood disclosed a red-cell count of 3,830,000, with a hemoglobin of 85 per cent, and a white-cell count of 24,300, with 87 per cent neutrophils, 12 per cent lymphocytes and 1 per cent basophils. Repeated urinalyses were negative except for a rare pus cell. A serologic test for syphilis, repeated 3 weeks later, was negative.

The patient was placed on 30,000 units of penicillin every 3 hours. No other medicine was given. In 96 hours the temperature had descended to a normal level, and the chest was clearing clinically and on x-ray examination. On the 3rd day, a nonitching rash appeared, consisting of minute, closely packed red points, nonpapular in character, involving all portions of the body more or less simultaneously. The oropharynx and tongue exhibited no lesions. No adenopathy or vomiting was present. Rumpel-Leede's sign could not be elicited. After 24 hours the penicillin was discontinued, and the rash began to fade. Within 3 days, all erythema had disappeared, and extensive desquamation occurred, persisting for 5 days.

Contact patch tests with soap and with rubbing alcohol were negative. Passive transfer tests with commercial penicillin and crystalline penicillin produced, on the test subject, wheals with pseudopods that reached diameters of 2.5 cm in 20 minutes and persisted for about 1 hour; serum and penicillin controls gave only areas of erythema about 0.6 cm in diameter. It was not practical to do intradermal skin tests on the patient.

Pyle⁴¹ has stated that in 4000 cases treated with penicillin he saw no rash similar to that observed in the case presented above. Goldman⁴² noted a similar reaction in a physician. Moore⁴³ stated that among 25,000 patients in the nation-wide syphilis study there were perhaps 4 such cases.

A review of the literature suggests that penicillin should not be used for minor ailments. Patients who have previously been treated with penicillin and those who have had previous fungous infections should be closely watched. Skin testing should help to warn the physician of a potential allergic reaction, although not all physicians would agree with Cormia⁸ that an immediate reaction 10 cm in diameter contraindicates penicillin therapy. In general it is a wise policy to begin a course of penicillin injections with small dosages, to prevent possible aggravation of foci of infection. If the patient has areas of fungous infection, they should be treated locally at the same time as the penicillin is administered intramuscularly. When penicillin is used topically or administered orally the possibility of a contact type of sensitivity should always be kept in mind.

SUMMARY

A review of the literature on allergic reactions to penicillin is presented, and a case of an apparent reaction is described. Caution in the administration of the drug for minor ailments is stressed, and the value of skin tests for sensitivity is discussed.

REFERENCES

1. Jadassohn W, Schaaf F, and Wohler, G. Analysis of composite antigens by Schultz-Dale technic further experimental analyses of trichophytins. *J Immunol* 32 203-227, 1937.
2. Florey M E, and Florey H W. General and local administration of penicillin. *Lancet* 1 387-397, 1943.
3. Keefer C S, Blake, F G, Marshall, E K, Jr, Lockwood, J S, and Wood W B, Jr. Penicillin in treatment of infections: report of 500 cases. *J A M A* 122 1217-1224, 1943.
4. Lyons, C. Penicillin therapy of surgical infections in U S Army report. *J A M A* 123 1007-1018, 1943.
5. Stokes J H, Sternberg T H, Schwartz, W H, Mahoney J F, Moore, J E, and Wood, W B, Jr. Action of penicillin in late syphilis including neurosyphilis, benign late syphilis and late congenital syphilis: preliminary report. *J A M A* 126 73-80, 1944.
6. Moore, J E, Mahoney J F, Schwartz, W, Sternberg, T, and Wood, W. Treatment of early syphilis with penicillin: preliminary report of 1,418 cases. *J A M A* 126 67-73, 1944.
7. Dawson, M H, and Hobby, G L. Clinical use of penicillin observations in 100 cases. *J A M A* 124 611-622, 1944.
8. Cormia F E, Jacobson, L Y, and Smith E. L. Reactions to penicillin. *Bull U S Army M Dept* 4 694-702, 1945.
9. Haswell R E, and Wilkinson, J F. Allergic reaction to parenteral penicillin. *Lancet* 1 308, 1946.
10. Herrrell W E, Nichols D R, and Heilman D H. Penicillin its usefulness, limitations, diffusion and detection, with analysis of 150 cases. *J A M A* 125 1003-1011, 1944.
11. Epstein, S, and Pinkus H. Penicillin dermatitis based on tuberculin type sensitivity: report of case with remarks on experimental sensitization to penicillin. *Ann Allergy* 4 186-195, 1946.
12. Pyle, H D, and Rattner H. Contact dermatitis from penicillin. *J A M A* 125 903, 1944.
13. Binkley, G W, and Brockmole, A. Dermatitis from penicillin report of two cases. *Arch Dermat & Syph* 50 326, 1944.
14. Satulsky, E M. Dermatitis venenata of eyes and eyelids from local use of penicillin. *J Soc New Jersey* 43 95, 1946.
15. Markson, L. S. Dermatitis venenata following use of penicillin ointment. *Arch Dermat & Syph* 52 384, 1945.
16. Bedford P D. Case of penicillin dermatitis. *Brit M J* 1 51, 1946.
17. Silvers S H. Contact dermatitis from amorphous sodium penicillin. *Arch Dermat & Syph* 50 328, 1944.
18. Benkwith, K B. Allergy to penicillin calcium topically in blepharconjunctivitis. *U S Nav M Bull* 46:279, 1946.
19. Schultz A. Ocular dermatitis from local penicillin report of two cases. *Arch Ophth* 35 145-149, 1946.
20. Barker, A N. Allergic reactions to penicillin. *Lancet* 1 177, 1945.
21. Michie, W, and Baile, H W C. Case of penicillin reaction. *Brit M J* 1 554, 1945.
22. Vickers, H R. Contact dermatitis caused by penicillin. *Lancet* 1 307, 1946.
23. Kleinfeld L. Sequelae following oral and topical use of penicillin. *New York State J Med* 46 915, 1946.
24. Phillips E. Glossitis and stomatitis due to penicillin lozenges and troches. *Permanent Found M Bull* 4 20-23, 1946.
25. Kern, E. C. Local reaction to penicillin given by mouth. *J Soc New Jersey* 42 326, 1945.
26. Selinger, E. Dermatitis of lids from penicillin eye drops. *J A M A* 128 437, 1945.
27. Goldman, L, Friend, F, and Mason, L M. Dermatitis from penicillin. *J A M A* 131 883-890, 1946.
28. Cripp, L H. Allergy to penicillin. *J A M A* 126 429, 1944.
29. Morris, G E, and Downing, J G. Bullous dermatitis (dermatitis medicamentosa) from penicillin. *J A M A* 127 711, 1945.
30. Strickland, D A. Penicillin sensitivity: angio-neurotic reaction. *U S Nav M Bull* 45 768, 1945.
31. Flinn, L B, McGee, L C, Featherston, A P, and Kern, D O. Skin lesions attending use of penicillin. *Delaware State M J* 17 133-135, 1945.
32. Truitt, G W. Reactions to penicillin. *Ann Allergy* 4 196-198, 1946.
33. Graves W N, Carpenter C C, and Unangut R W. Recurrent vesicular eruptions appearing during administration of penicillin. *Arch Dermat & Syph* 50 6, 1944.
34. Lamb, J H. Allergic reactions during administration of penicillin. *Arch Dermat & Syph* 52 93-95, 1945.
35. Heinlein, J A, Carpenter, C C, and Duffy B J, Jr. Aggravation of bacterids by penicillin with theory as to causation. *U S Nav M Bull* 46:571-575, 1946.
36. Price I C. Severe allergic reaction to intramuscular penicillin. *Canad M A J* 53 485, 1945.
37. Sullens W E, Jr. Simulating serum sickness reaction to penicillin. *U S Nav M Bull* 45 752-754, 1945.
38. Welch H, and Rostenberg, A, Jr. Hypersensitivity of tuberculin type to crystalline penicillin sodium. *J A M A* 126 10-12, 1944.
39. Rostenberg A, Jr., and Welch H. Study of types of hypersensitivity induced by penicillin. *Am J M Sc* 210 158-167, 1945.
40. Clayton, I H. Cited by Goldman et al.⁴¹
41. Pyle H D. Personal communication.
42. Goldman L. Personal communication.
43. Moore, J E. Personal communication.

each with its own branch office and full-time physician in charge of physical medicine and medical rehabilitation. The branch areas similar to the central office have consultants, if possible, for physical medicine and rehabilitation in each area. Further subdivision is on the level of the hospitals, in which a chief of physical medicine is responsible for rehabilitation. Under him is an executive officer ordinarily with experience in rehabilitation in the Army or Navy. Technical services are divided into various categories, such as physical therapy, occupational therapy, physical reconditioning, educational retraining and shop retraining. The chief of physical medicine is responsible for prescribing treatment for patients in one or all of these sections, depending on individual physical and mental needs. Only physical and occupational therapists who are properly qualified may receive professional ratings and are given new appointments. Members of the technical staff in physical reconditioning, shop retraining and educational retraining are also required to have special qualifications by education and previous experience in these fields.

It is apparent that a more varied and graded treatment is available for convalescent patients in the Veterans Administration than in any civilian hospitals, with the possible exception of the better mental institutions. The success of this program can be achieved only when the entire medical staff is aware of its existence and cognizant of the proper selection of patients for referral. Plans have therefore been made to establish regular rehabilitation conferences of representatives of the various units mentioned above, together with social-service workers, psychiatrists, psychometrists and the ward officers, so that a total plan of rehabilitation can be mapped out for the patients. Further education of the general-hospital staff is provided by staff conferences and bulletins. Because the value of this rather elaborate and expensive setup for rehabilitation can be measured only by results, all the chiefs of physical medicine have been asked to devise new forms for recording progress and results. By this means new records now being distributed may, if properly utilized, help to evaluate the success of this important work.

The most rapid progress has been made in the mental institutions where the members of the staff are already familiar with many of the procedures of rehabilitation, such as shop work. The difference in the present goal, however, is that this type of therapy is aimed at directing the patient toward economic independence and complete social as well as physiologic recovery. Contacts with industry are therefore made, and already an appreciable number of patients have successfully taken their place in industry from mental hospitals as a direct result of this rehabilitation program.

At present, the plan of organization calls for physical and occupational therapy, physical reconditioning,

shop retraining and educational retraining in the various types of hospitals, such as general medical and surgical, tuberculosis and neuropsychiatric. It is too early to determine exactly the significance of the treatment, but the psychiatrists are doing clinical research to evaluate the results in the different types of hospital.

It is also the plan of the Veterans Administration to affiliate the hospitals whenever possible as teaching units of adjacent medical schools. This should be of benefit for the medical schools as well as for the Veterans hospitals, particularly in physical medicine, since the students will be able to see rehabilitation in action.

CIVILIAN REHABILITATION

There is considerable statistical evidence that rehabilitation of industrial casualties and other civilians with physical handicaps is financially sound. In the relatively few cities in the United States where community rehabilitation centers are already established, much is being achieved by treatment of the injured patient during convalescence after the acute surgical stage, bringing him on to the point of re-employment. An apparent growth of social responsibility for the disabled is manifested by the Vocational Rehabilitation Act, which provides for the purchase of medical and surgical services for physical restoration of patients who may become employable by such treatment and are in financial need. There are, however, insufficient facilities at present to provide these services, since the average civilian hospital is not equipped to render treatment during the entire convalescent period because of lack of physical facilities and trained personnel. Physicians in general are little acquainted with the possibilities of such treatment and still refer patients to such facilities, even when available, only after months of ineffectual treatment. The medical schools, in general, are also doing nothing to train future physicians in this type of service.

Experience obtained from centers established in England and in the armed forces in the United States has made it possible to outline functional physical medicine and medical rehabilitation adaptable to civilian practice¹⁴⁻¹⁶. The first point is the introduction of physical reconditioning into every ward from the first stage of recovery from disease or injury, without allowing the patient the mental and physical deterioration from excessive inactivity. The second point is establishment of a plan of convalescence to speed recovery of physical and psychologic function. Thirdly, the form of treatment for rehabilitation must be adapted individually for the patient's disability as measured by careful functional tests. Another important point in the success of treatment is personal supervision by a properly trained physician through the entire program, that is, until the patient is placed in society and industry, when possible.

The basic principles on which this plan of rehabilitation is organized are those of a system of restoration of mental and physical functions by physical and mental activity. It has been stressed that the art of rehabilitation is making the patient do his exercises regularly, efficiently and, above all, willingly, since there is no greater fatigue than that of boredom. The mental problem in rehabilitation is repeatedly emphasized. For this reason, it has been advocated that the center be functionally allied to hospitals, although geographically separate, so that the patient may be stimulated to self-endeavor in an atmosphere of enthusiasm coupled with a feeling of well-being, rather than the atmosphere of a hospital. It is taken for granted that there is continual progress and enthusiasm in such centers. O'Malley advocates a residential center accommodating 200 to 250 patients. Of the accommodations necessary beyond that of domestic facilities, first and foremost is a large gymnasium. In connection with this are the doctors' consulting rooms, secretaries' offices, cafeteria, physical-therapy rooms, swimming pool, rest rooms and sun terraces. Smaller gymnasiums are also advised for more individual treatment of patients with acute injuries. Outside the gymnasium there should be playing fields and also a library and other recreational facilities, such as a hall for dances, motion pictures, lectures, concerts and theatricals. Because the success of the work depends so much on the morale of both the staff and the patients, the right type of leadership and personality in the staff is stressed. Proper reception of the patients is thought to be of considerable importance on the principle "that if you want to keep a cat in the house you must butter its feet." Attempts at establishing a proper *esprit de corps* are begun at once.

The organization of the staff in this center consists of a commanding officer, or director, and three medical officers for each 250 patients. Under them are the physical-fitness officer and physical-training instructors, who are responsible for the exercise classes. The patients are classified according to injury groups, of which there are four main divisions — two in which the lower limbs are involved, and one each for injuries of the arms and spine — that, in turn, are graded according to degree of convalescence and ability to perform exercises. Physical therapists are used, but the emphasis is on exercise rather than on passive procedures, the early groups exercising first on the anatomic and later on the functional approach and finally for maximum efficiency. In the occupational-therapy section the work is partly diversional and partly remedial, aiming toward vocational training.

Remedial exercises have been divided into a direct and an indirect approach, the former comprising the exercises and treatments in the physiotherapy room, with a maximum time limit of about thirty minutes for this type of treatment, and the latter

including swimming, cycling, clay-pigeon shooting, archery, roller skating, and games such as badminton and volley ball. The responsibility of grading, which is an important function, is left to the medical officer, since it has been found that premature removal of a patient into more advanced groups is as harmful as too prolonged periods in low groups.

The mental and social aspects are thought to comprise nearly 75 per cent of the problem, and the solution is afforded by the environment of the center and the personalities of the staff, as well as by a proper design for living — that is, a balanced program including light recreational activities together with more serious educational and vocational guidance.

The results of this program are of interest. In the unit reported by O'Malley approximately 10,000 injured persons were seen in a three-year period, 92 per cent of the injured air crews returned to duty, 64 per cent to the actual operation of flying, and 84 per cent of the technicians returned to their trade. In view of these results similar ventures are advocated for civilian life, and many of these are in actual operation.

Programs for convalescent care and rehabilitation in the Army Air Forces, Army and Navy have received considerable publicity in the medical and lay press.⁴⁻¹¹ The treatment for the convalescent patient starts while he is still in bed with physical reconditioning composed of short daily periods of light bed exercise designed to allay muscle atrophy in parts of the body not diseased or injured. At the same time educational reconditioning is begun, including organized lectures and group discussions. Thirdly, occupational therapy, consisting of light purposeful tasks, creative art or handicraft, such as leather working and wood carving, has been found of assistance in restoring function and is of benefit for morale. For ambulatory patients physical reconditioning is more strenuous, including calisthenics, gymnastics and athletic sports. At the same time the occupational therapy is graded for heavier work. Finally, physical training leads to conditioning for extreme physical exertion, and the educational retraining directs the patient by refresher courses in military training, including map reading, scouting, use of weapons and so forth. This educational retraining is adapted to the special needs of the patient.

REHABILITATION OF VETERANS

The rehabilitation of veterans is a problem of general interest, and the plans now in operation are worthy of more detailed consideration.^{12, 13} The organization includes a central office in Washington in charge of physical medicine and medical rehabilitation that receives the advice of a national consultant. The country is then divided into branches roughly corresponding to the Army areas,

et al²⁵ from tests on normal control subjects. The conclusions, in part, were as follows:

The most important single element in the intensification of the daily volitional work output is the will to perform with physiologically maximum effort. Augmentation in strength through daily exercise is associated with significant increase in the work done on the limit day. The rate of improvement in work capacity is rapid under a program of heavy resistance exercise. Strength may more than double in four weeks with systematic training. There is no evidence of significant loss in the kind of increase in work capacity which is acquired by heavy resistance exercise during the post-exercise period which exceeds in duration the initial period of training. The ability to perform work may continue to improve after the cessation of systematic training. This phenomenon suggests changes of an unexplained kind associated with motor learning among which must be included significant extension of the psychological end point of fatigue.

In view of these early reports of success in this method of exercise therapy, a study of its use in various pathologic conditions is warranted. Its possible value in the treatment of poliomyelitis is at present being studied.

Other specialized exercise technics have been developed in the therapy of diseases of special parts of the body. For example, systematic preoperative and postoperative exercises have been found to be of value for patients subjected to chest surgery, particularly thoracoplasty. The greatest success is obtained when exercises are started preoperatively with explanations to the patient of what his postoperative problems will be. These include the mobility of the shoulder and scapula and the function of the supporting musculature of these parts, proper breathing and posture. Actual details of procedures to be used have been reported by several authors.²⁶⁻²⁸

Correct posture and body mechanics has continued to receive the interest of orthopedists and physical therapists, particularly because of its preventive implications.²⁷ Quantitative methods of evaluation have been described.²⁸ The dynamics of posture have been emphasized by Howarth.²⁹ He pointed out the changes during infancy, childhood and adult life and the variations in sitting, standing and lying positions that are generally encountered. The advantage of good basic dynamic position is stressed in athletics as well as in everyday life, and the acquisition of such control is thought to be rewarding in the reduction of fatigue, avoidance of accidents and even as an "approach to life."

One aspect of therapeutic exercise is instruction of patients in the use of crutches. Although the usefulness of these aids to ambulation is generally accepted, little information is readily available in the literature for instruction of students, physical therapists, patients or physicians. Deaver and his associates³⁰⁻³² have recently published detailed articles with illustrations showing the proper use of crutches for various conditions. These papers have also been reprinted in a monograph that is a

definite contribution to the literature of physical medicine.

COMBINED DRUG AND PHYSICAL THERAPY

Other procedures in physical medicine that have received considerable attention include the combined use of certain drugs that have an effect on neuromuscular function and exercise therapy. Curare which is known to have an inhibitory effect on neuromuscular transmission, has been used to reduce spasticity in central-nervous-system diseases, such as hemiplegia and infantile cerebral palsy. To provide for prolonged effect a suspension of curare in a mixture of peanut oil and wax has been said to provide relaxation of muscle spasm up to three days' duration.³³⁻³⁵ With such a method of administration the unpleasant side effects were absent. Maximum benefit from the drug was obtained when physical therapy was also administered to increase function when spasticity was reduced. This combination of curare and therapeutic exercise, according to Schlesinger,³²⁻³⁵ is most effective in cases in which some voluntary function is present, rather than in paraplegic patients with spasticity and no active motion.

Schlesinger and Ragan³⁴ have also reported beneficial effects from curare in the treatment of muscle spasm of other origin, particularly that associated with acute low-back pain. Jones³⁵ states that curare may be used to help in the differential diagnosis of muscle spasm of reflex origin from that due to organic changes in limitation of passive motion or in the joints. It has also been suggested that curare is of value in the differentiation of pain due to nerve-root irritation and that secondary to inflammation of joints and surrounding tissue; the former is not affected by curare, and the latter is relieved. Although considerable lax excitement has been instigated by reports of remarkable success from this combination of curare and physical therapy in the treatment of spastic conditions, in my opinion its true worth will be known only after careful clinical analysis. Almost all patients who have previously had little or no treatment are benefited when given systematic physical therapy, particularly when their hopes are keyed up so that co-operation in the program is good. Just how much of the success of treatment is dependent on curare and how much on the physical therapy and how much is due to the combination will be known when more complete reports are published.

Curare has also been used in the treatment of infantile paralysis in a few clinics, with conflicting reports.³⁶⁻³⁷ The rationale of using a drug that is known to cause loss of voluntary muscle control in a disease that causes flaccid paralysis of muscles is not apparent to most physicians. Although it may be possible to relieve meningismus and other types of muscle hyperirritability present in the acute stage,

One of the simplest and most obvious means of combating disuse atrophy from bed rest has been the adoption of early rising following surgical procedures and in the puerperium. A number of reports on this subject have appeared in the literature, the consensus being that early rising is not dangerous but, in fact, reduces the incidence of complications, particularly those of thrombophlebitis and phlebothrombosis with pulmonary emboli. Convalescence is markedly speeded by this practice, which is of special value in these times of shortage of hospital beds.¹⁷⁻²² In addition to early rising, leg exercises with special mechanical apparatus have been devised, particularly to reduce the incidence of pulmonary embolism secondary to venous thrombosis.²³ It has also been pointed out that simply getting the patient out of bed is not sufficient to protect against venous clotting, for to allow a patient to sit in a chair with the legs dependent causes greater circulatory stasis in the veins of the lower extremity than that produced if he contracts his musculature actively against resistance lying in the horizontal position. Early rising and ambulation, to be effective, require that the patient walk.²⁴

The principle of separation of the rehabilitation from the hospital has been stressed in the armed forces for reasons of morale. As Hellebrandt²⁵ has pointed out, this separation is less urgent in civilian practice, where much may be gained by the close supervision of a resident medical staff if the rehabilitation section is connected with the hospital. A physical-medicine specialist in constant attendance is desirable for proper supervision of the treatment. Because of the tradition of not allowing patients to do things for themselves in general hospitals, some changes may be necessary in rehabilitation wards, as pointed out by Deaver.¹⁷ He has emphasized the importance of functional education to teach fundamental activities and skills beginning with the most commonplace and humble acts. Patients such as paraplegics and hemiplegics may be graded according to their ability to perform the everyday activities of life, and simply by the act of grading performances their competitive spirit may be aroused, with the result that they are stimulated to more rapid recovery.

One of the most striking advances in rehabilitation concerns the treatment of patients paralyzed by injuries of the spine—that is, the paraplegic patients.²⁶⁻²⁹ Special services to take care of these patients were developed in the armed forces, where the importance of teamwork was emphasized. The surgical care was handled by the neurosurgeon, orthopedic surgeon and urologic specialist. The patient must also be watched carefully for general nutrition by the medical specialist, and his skin taken care of by the nursing staff. With proper treatment it has been found possible to save the lives of paraplegic patients and, with the help of the medical-rehabilitation department, to teach the ma-

jority to be self-sufficient to a remarkable degree. Most of them can be taught to walk with crutches, even those with severe flexor spasms being relieved by anterior rhizotomy.³⁰ Compensatory development of the upper extremities, under the supervision of physical rehabilitationists, aids the patient in learning to walk under the direction of a physical therapist. Skills are developed first by the occupational therapist, and later in the shop retraining department, so that actual vocational training is achieved. Contacts with industry have been made in many of the hospitals so that patients may be gainfully employed while still in the hospital and on discharge. Morale has been fortified by grouping patients with similar injuries in centers where improvement is placed on a competitive basis, including individual scoring systems.

Centers have also been admirably developed for the care of amputees. Again, general physical development is stressed, and proper use of prostheses taught, including ambulation and vocational training.³¹ There are, however, many more amputees in civilian practice than resulted from war injuries, and the fine results achieved in service hospitals remain as a challenge for better treatment in civilian practice.

NEW TECHNIQUES

In view of the considerable emphasis on rehabilitation, particularly early return of function in diseased and injured extremities, it is understandable that the greatest interest in physical-therapy techniques has recently concerned exercise therapy. The method that has perhaps attracted the most attention is that of systematized weight lifting adapted to therapeutic exercise. DeLorme³² developed in the Army a program of heavy-resistance, low-repetition exercise based on the technic of weight lifters. This was found to be extremely effective in developing muscle strength following traumatic lesions of the bones, joints and surrounding tissues. This system of training can be briefly summarized as follows: individual exercises with a load heavy enough to preclude more than ten to fifteen successive contractions, an increase in resistance as soon as the load can be lifted ten consecutive times with ease, periodic attempts to surpass and improve the maximum performance, and rest periods in relation to the day of maximum performance for testing.

Applying these principles of weight lifting, DeLorme devised an apparatus that was mechanically suitable for exercising all the major muscle groups of the trunk and extremities. He reported signal success in increasing strength of the muscle groups so exercised, together with actual hypertrophy as judged by circumferential measurements.

It is well known that such methods, although empiric in origin, are successful in developing the strength of normal persons. Some investigations to explain these results have been made by Houtz

physical fitness, and there was similarly a higher increase in lactate following a grip test, with an output of more electric discharges from the muscles when measured electromyographically.

The search for improvements in measurements of fitness still continues, one of the most recent being based on the change in the reduction time of blood after breath holding.⁶⁰ Others have emphasized the value of skill and the psychologic factors in evaluating working capacity, particularly of the physically impaired. Such measurements are essential to the successful working of rehabilitation programs resulting in correct placement in industry.⁶¹⁻⁶³

Electrophysiology

Studies are still reported on technics of electric stimulation and the effects of such stimulation on atrophy of denervation and disuse. Many different wave forms have been used for stimulating nerve and muscle, such as the sine wave, exponentially following currents, inductive impulses and square waves. Offner⁶⁴ calculated on the basis of heat production that that wave form causing excitation with minimum injury was an exponentially rising current. Because such a current is not readily produced by simple electronic circuits, the next best wave form for clinical use is the square wave, sine waves being the least efficient, requiring 85 per cent more power than the most efficient type.

Fischer and Ramsey⁶⁵ found that daily electric stimulation of denervated rabbit muscle was effective in retarding weight loss and deterioration of muscle protein. Treatment applied against high resistance was more effective than when the muscle contracted freely or against little resistance. A study of protein concentration and atrophy due to tenotomy disclosed that the changes were practically the same as those following denervation.⁶⁶ The atrophy of demobilization alone was nearly as great as that from the other two conditions, but the total protein concentration loss was only about a third. Ko man, Osborne and Ivy⁶⁷ also found that appropriate electric stimulation favorably altered the course of degeneration after crushing of the sciatic nerve in rats. Young⁶⁸ reported that muscle atrophy developed in the absence of either stimulation from above or resistance from below, both factors being essential for hypertrophy. Massage of denervated muscle, according to Sushind et al.,⁶⁹ caused only slight retardation of weight loss but was effective in maintaining the strength. Electric stimulation retarded weight loss but exerted no effect on the contractile strength per unit mass of muscle. It was concluded that effective therapy for treatment of paralyzed muscles is a combination of electric stimulation and massage.

REFERENCES

1. Current Comment. *Physiatrist*. *J A M A* 131:54 1946
2. Watkins A. L. Research in physical medicine. *Ann Eng J Med*. 234:550-552 628-634 1946
3. O'Malley C. I. S. Medical rehabilitation. *Br J Phys Med* 9:157-174 1946
4. Thorndike A. Reconditioning for war wounded. United States Army Service Forces program. *Am J Surg* 67:302-315 1945
5. Rusk H. A. Convalescent care and rehabilitation in Army Air Forces: new challenge of postwar medicine. *M Clin North America* 29:15-72b 1945
6. Montgomery H. H. Rehabilitation in Navy. *Arch Phys Med* 26:214-219 1945
7. Dines J. B. Rehabilitation of war casualties. *Nat Med* 7:32-35, 1945
8. Kenard W. J. Experiences in AAF convalescent program. *Rosky Mountain M J* 42:181-185 1945
9. Lowman E. W. Planned convalescence. *U S Air M Bull* 43:611-620 1944
10. Huddleston O. L. Physical therapy and reconditioning therapy at Fitzsimons General Hospital Denver. *Arch Phys Med* 27:11-17 1946
11. Bronner F. Analysis of role and function of educational reconditioning with particular reference to program of Welch Convalescent Hospital. *Occup Therapy* 25:99-110 1946
12. Corale D. A. Medical rehabilitation program in Veterans Administration. *Occup Therapy* 25:123-127 1946
13. Grossman M. Coordinating occupational therapy and physical medicine in Veterans Administration hospitals. *Occup Therapy* 25:118-122 1946
14. Patterson J. W. T. Physical medicine in Army: its effect on civil practice. *Brit J Phys Med* 8:155-163 1945
15. Ward F. G. Rehabilitation in post war period. *Brit J Phys Med* 9:38-42 1946
16. Miller A. Rehabilitation of disabled: sociological study. *Brit J Phys Med* 9:2-7 1946
17. Deaver G. G. Functional education in rehabilitation. *S Clin North America* 25:374-381 1945
18. King A. G. Early puerperal rising. *Am J Obst & Gynec* 52:657-660 1946
19. Headings D. M. and Palmer R. E. Relation of early rising to morbidity in cesarean section. *Am J Obst & Gynec* 52:661-664 1946
20. Bodgett J. B. and Beatrice E. J. Early postoperative rising: statistical study of spinal complications. *Surg Gynec & Obst* 82:485-489 1946
21. Rosenblum G. Melnikoff E., and Fiat H. S. Early rising in puerperium. *J A M A* 129:849-850 1945
22. Fitzgibbon G. Post-operative activity and resumption of normal movement: their influence on embolism and thrombosis. *Brit M J* 2:413-416 1946
23. Narat J. A. and Cipolla A. F. New method of leg exercises. *Arch Surg* 53:343-347 1946
24. Ochsner A. Venous thrombosis. *J A M A* 132:827-833 1946
25. Hellebrandt F. A. Adaptability of present day concepts of convalescent training and physical rehabilitation to civilian practice of medicine. *Arch Phys Med* 27:1-6-140 1946
26. Botterell E. H. Jousse A. T. Aberhart C. and Cluff J. W. Paraplegia following war. *Cared M J* 35:249-259 1946
27. Kennedy R. H. New viewpoint toward spinal cord injuries. *Ann Surg* 124:1057-1065 1946
28. Guttmann L. Rehabilitation after injuries to spinal cord and cauda equina. *Brit J Phys Med* 9:10-157 1946
29. Elkins C. W. and Wegner W. R. Newer concepts in treatment of paralyzed patient due to war-time injuries of spine. II. Neurosurgical complications. *Ann Surg* 123:516-522 1946
30. Munro D. Rehabilitation of patients totally paralyzed below waist, with special reference to making them ambulatory and capable of earning their living. I. Anterior rhizotomy for spastic paraplegia. *Ann Eng J Med* 233:453-461 1945
31. Editorial. Physical therapy management of lower extremity amputees. *Bull U S Army Med Dept* 5:623 1946
32. DeLorme T. L. Heavy resistance exercises. *Arch Phys Med* 27:607-610 1946
33. Houtz S. J. Parrish A. M., and Hellebrandt F. A. Influence of heavy resistance exercise on strength. *Physiotherapy Res* 26:299-304 1946
34. Harken D. E. Review of activities of thoracic center for III and IV hospital groups. 160th General Hospital European Theater of Operations, June 10 1944 to Jan 1 1945. *J Thoracic Surg* 15:41-43 1946
35. Winston H. R. Physical therapy and chest surgery. *Physiotherapy Res* 26:227-230 1946
36. Huddleston O. L. Aspects of physical therapy and reconditioning in some of army hospitals. *Clinics* 1:174-181 1946
37. McDonnell J. Sleep posture: its implications. *Brit J Phys Med* 9:46-52 1946
38. Kraus H. and Eisenmenger-Weber S. Quantitative tabulation of posture evaluation based on structural and functional measurements. *Physiotherapy Res* 26:2-242 1946
39. Howarth B. Dynamic posture. *J A M A* 131:1399-1404 1946
40. Deaver G. G. and Brown M. E. Challenge of crutches. V. Daily activities on crutches. *Arch Phys Med* 27:141-157 1946
41. Idem. Challenge of crutches. VI. Living with crutches and canes. *Arch Phys Med* 27:683-703 1946
42. Schlesinger E. B. Recent advances in use of curare in clinical practice. *Bull New York Acad Med* 22:50-529 1946
43. Idem. Use of curare in oil in treatment of spasticity following injury of spinal cord. *Arch Neurol & Psychiat* 55:30-34 1946

its value in reducing residual paralysis can be determined only by further study

Neostigmine (prostigmine) is another drug that has recently received a great deal of publicity because of reported benefits in relieving muscle spasm, particularly when combined with the usual types of physical therapy. There can be no doubt that this drug acts to stimulate the intestinal tract and has striking clinical beneficial effects in relief of the symptoms of myasthenia gravis. The increase of muscle strength, which is striking in these patients, is thought to be due to the inhibition of cholinesterase, which is the agent destroying acetylcholine, an important factor in neuromuscular transmission. The action is primarily at the myoneural junction, but there is some evidence of effects in spinal centers, particularly relief of spasticity in patients with spinal-cord disease or hemiplegia. This drug has accordingly been tried in a wide variety of diseases in which there is evidence of muscular spasm, spasticity, cramps or pain. One group has reported beneficial results in poliomyelitis, rheumatoid arthritis, cerebral palsy, hemiplegia, facial paralysis, subacromial bursitis and similar conditions as judged by clinical response, together with the use of physical therapy.^{48, 49} Clinical appraisal of beneficial results seems to be lacking in the early reports, and, as is often true, later studies are beginning to show negative results—for example, in the treatment of rheumatoid arthritis.⁵⁰

RESEARCH

Fitness Tests

Although research in physical medicine has recently been reviewed, the increasing emphasis on exercise therapy justifies a summary of some of the latest studies on testing physical fitness. Physical-training programs were developed to a remarkable degree during the war with the hope of increasing capacity for physical exertion and also efficiency in activities not requiring much physical exertion, such as piloting aircraft. To assess the value of these programs it is necessary to develop methods of measuring physical fitness. This subject has been reviewed by Johnson,⁵¹ of the Harvard Fatigue Laboratory. He has pointed out that if unquestionably fit and unfit men of similar stature are compared while performing the same work, which they are able to sustain in a steady state, the fit men show a greater oxygen consumption, a slower pulse rate, a lower systolic blood pressure, a larger stroke volume and a lower blood lactate during work and a faster return of the blood pressure and pulse rate to resting value after work. If the work is too much to be maintained steadily, the fit man shows a longer duration of effort before exhaustion, a higher oxygen consumption, a somewhat slower maximal pulse rate, a larger stroke volume, a higher blood lactate and a faster return of the blood pressure to normal after work. In other words, the man who was said to

be fit carries on moderate work with less disturbance of physiologic equilibrium. When forced, he can displace this equilibrium farther and for a longer time, and his recuperative powers are such that after exhausting exercise he returns to normal more quickly.

The physical-fitness tests most widely used tax the cardiovascular system by exercises involving large muscle groups without demanding unusual types of skill, as in the step test, treadmill and bicycle ergometer.^{52, 53} The most frequent measurements are oxygen consumption, pulse rate, blood pressure and blood lactate. An important difficulty in all such measurements is that the patient must have motivation to do well. The ideal test would therefore eliminate the psychologic factor. These tests have been used fairly successfully in the measurement of physical conditions before and after periods of training. The conclusions from these studies are that it is impossible at present to predict by a single examination how much a given subject is capable of improving with training and that men in reasonably good condition at the start of the program require more vigorous training to improve significantly than men in poor condition.⁵⁴

Significant clinical applications of these physical fitness tests have been made in progress of rehabilitation and convalescence. Landis⁵⁵ has pointed out the value of adjustment to the peripheral circulation encountered during convalescence. His physiologic analysis gives weight to the importance of early supervised exercises performed by patients while still in bed, followed by more active physical reconditioning during convalescence. Karpovich, Starr and Weiss⁵⁶ reported speeded convalescence by physical-training programs during which the degree of activity was determined by graded step tests. Physical-fitness tests have also been used in studies of neurocirculatory asthenia, effort syndrome and fatigue states. During exercise on the bicycle ergometer it has been found by some workers that there was a significantly poor exercise response in the psychoneurotic patients as compared with normal controls.⁵⁷ Oxygen uptake, lactate rise and pulse rate were determined, and oxygen consumption was considered the most satisfactory quantitation of exercise response. Cohen et al.⁵⁸ observed abnormally small displacement of homeostasis with maximal effort and abnormally large displacement with moderate work, indicating poor physical condition. They suggested that this intolerance to effort was due to constitutional inferiority. Both psychologic and physiologic studies in psychoneurotic patients complaining chiefly of fatigue were carried out by Watkins and his associates,⁵⁹ who noted that certain psychologic states seemed to precipitate or consistently preceded the onset of fatigue. In the same group of patients submaximal work on the bicycle ergometer was accompanied by abnormally high lactate values that may have indicated poor

physical fitness, and there was similarly a higher increase in lactate following a grip test, with an output of more electric discharges from the muscles when measured electromyographically.

The search for improvements in measurements of fitness still continues, one of the most recent being based on the change in the reduction time of blood after breath holding.⁶⁰ Others have emphasized the value of skill and the psychologic factors in evaluating working capacity, particularly of the physically impaired. Such measurements are essential to the successful working of rehabilitation programs resulting in correct placement in industry.⁶¹⁻⁶³

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REFERENCES

1. Current Comment. *Physiatrist*. *J A M A* 131:34 1946
2. Watkins A L. Research in physical medicine. *New Eng J Med* 234:64-500 and 628-634 1946
3. O Malley, C J S. Medical rehabilitation. *Brit J Phys Med* 9:137-145, 1946
4. Thorndike A. Reconditioning for war wounded. United States Army Service Forces' program. *Am J Surg* 67:302-318 1945
5. Rust H A. Convalescent care and rehabilitation in Army Air Forces new challenge of postwar medicine. *M Clin North America* 29:715-728 1945
6. Montgomery, H H. Rehabilitation in Navy. *Arch Phys Med* 26:214-219 1945
7. Dvnes, J B. Rehabilitation of war casualties. *War Med* 7:32-35, 1945
8. Kennard, W J. Experiences in AAF convalescent program. *Rocky Mountain M J* 42:181-188 1945
9. Lowman E W. Planned convalescence. *U S Air M Bull.* 43:611-620, 1944
10. Huddleston O L. Physical therapy and reconditioning therapy at Fitzsimons General Hospital, Denver. *Arch Phys Med* 27:11-17, 1946
11. Bronner, F. Analysis of role and function of educational reconditioning with particular reference to program of Welch Convalescent Hospital. *Occup Therapy* 25:99-110 1946
12. Covalt D A. Medical rehabilitation program in Veterans Administration. *Occup Therapy* 25:123-127 1946
13. Grossman, M. Coordinating occupational therapy and physical medicine in Veterans Administration hospitals. *Occup Therapy* 25:118-122 1946
14. Patterson J W T. Physical medicine in Army its effect on civil practice. *Brit J Phys Med* 8:158-163 1945
15. Ward F G. Rehabilitation in post war period. *Brit J Phys Med* 9:38-42 1946
16. Miller A. Rehabilitation of disabled sociological study. *Brit J Phys Med* 9:27 1946
17. Deaver G G. Functional education in rehabilitation. *S Clin North America* 25:374-381 1945
18. King A G. Early puerperal rising. *Am J Obst & Gynec* 52:657-660 1946
19. Headings D M, and Palmer R E. Relation of early rising to morbidity in cesarean section. *Am J Obst & Gynec* 52:661-664 1946
20. Blodgett J B and Beatue E J. Early postoperative rising statistical study of hospital complications. *Surg Gynec & Obst* 82:485-489 1946
21. Rosenblum G, Melinkoff E and Fitt, H S. Early rising in puerperium. *J A M A* 129:849-853 1945
22. Fitzgibbon G. Post-operative activity and resumption of normal movement their influence on embolism and thrombosis. *Brit M J* 2:413-416, 1946
23. Narat J K and Cipolla A F. New method of leg exercises. *Arch Surg* 53:345-347, 1946
24. Ochsner A. Venous thrombosis. *J A M A* 132:827-833 1946
25. Hellebrandt, F A. Adaptability of present day concepts of convalescent training and physical rehabilitation to civilian practice of medicine. *Arch Phys Med* 27:136-140 1946
26. Botterell E H, Jousse, A T., Aberhart, C., and Cluff, J W. Paraplegia following war. *Canad M J* 4:35-249 1946
27. Kennedy R H. New viewpoint toward spinal cord injuries. *Ann Surg* 124:1057-1065, 1946
28. Gottmann L. Rehabilitation after injuries to spinal cord and cauda equina. *Brit J Phys Med* 9:130-137 1946
29. Elkins C W and Wegner W R. Newer concepts in treatment of paralyzed patient due to war-time injuries of spine II Neurosurgical complications. *Ann Surg* 123:516-521 1946
30. Munro D. Rehabilitation of patients totally paralyzed below waist with special reference to making them ambulatory and capable of earning their living I. Anterior rhizotomy for spastic paraplegia. *New Eng J Med* 233:453-461 1945
31. Editorial. Physical therapy management of lower extremity amputees. *Bull U S Arm, Med Dept* 5:623 1946
32. DeLorme T L. Heavy resistance exercises. *Arch Phys Med* 27:60-630 1946
33. Houtz, S J, Parrish A M and Hellebrandt, F A. Influence of heavy resistance exercise on strength. *Phys Therapy Rev* 26:299-304 1946
34. Harken D E. Review of activities of thoracic center for III and IV hospital groups 160th General Hospital European Theater of Operations June 10 1944 to Jan 1 1945. *J Thoracic Surg* 15:31-43 1946
35. Winston H R. Physical therapy and chest surgery. *Physiotherapy Rev* 26:227-230 1946
36. Huddleston O L. Aspects of physical therapy and reconditioning in some of army hospitals. *Curtis* 4:1674-1615 1946
37. McDonnell J. Sleep posture its implications. *Brit J Phys Med* 9:46-52 1946
38. Kraus H and Eisenmenger-Weber S. Quantitative tabulation of posture evaluation based on structural and functional measurements. *Physiotherapy Rev* 26:235-242 1946
39. Howarth B. Dynamic posture. *J A M A* 131:1399-1404, 1946.
40. Deaver G G and Brown M E. Challenge of crutches V. Daily activities on crutches. *Arch Phys Med* 27:141-157, 1946
41. *Idem*. Challenge of crutches VI. Living with crutches and canes. *Arch Phys Med* 27:683-703 1946.
42. Schlesinger E B. Recent advances in use of curare in clinical practice. *Bull New York Acad Med* 22:520-529 1946
43. *Idem*. Use of curare in oil in treatment of spasticity following injury of spinal cord. *Arch Neurol & Psychiat* 55:4:534 1946

- 44 Schlesinger, E B and Ragan, C "Muscle spasm" in acute low back pain and similar syndromes: new method of treatment with curare (d tubocurarine in oil and wax) *Am J Med* 1 621-627, 1946
- 45 Jones, C W Le Compte, C B and Kabat, H Studies on neuromuscular dysfunction. VIII. use of curare to differentiate muscle spasm from organic changes in limitation of passive motion at joints. *South M J* 39 799-801, 1946
- 46 Fox, M J Curare in treatment of acute poliomyelitis. *J A M A* 181 278-280, 1946
- 47 Ranschoff, N S Curare and intensive physical therapy in treatment of acute anterior poliomyelitis. *Bull New York Acad Med* 23 51-54, 1947
- 48 Kabat, H and Jones, C W Studies on neuromuscular dysfunction. Neostigmine therapy of chronic spastic paralysis from cerebral lesions. *J Nerv & Ment Dis* 103 107-129, 1946
- 49 Idem Studies on neuromuscular dysfunction. V. Neostigmine therapy of acute and chronic backache. *Arch Phys Med* 27 203-218, 1946
- 50 Balboni, V G Hollander, J L, and Kydd, D M Effect of prostigmine (neostigmine) on muscle spasm of rheumatoid arthritis. *Am J M Sc* 212 153-158, 1946
- 51 Johnson, R E Applied physiology. *Ann Rev Physiol* 8 535-558, 1946
- 52 Elbel, E R and Green, E L Pulse reaction to performing step-up exercise on benches of different heights. *Am J Physiol* 145 521-527, 1946
- 53 Erickson, L Simonson, E Taylor, H L, Alexander, H and Keys, A Energy cost of horizontal and grade walking on motor driven treadmill. *Am J Physiol* 145 391-401, 1946
- 54 Brouha, L Fradd, N W, and Savage, B M Studies in physical efficiency of college students. *Research Quart* 15 211-224, 1944
- 55 Landis, E M Circulatory adjustments peripheral circulation. *Federation Proc* 3 228-231, 1944
- 56 Karpovich, P V Starr, M P and Weiss, R A Physical fitness tests for convalescents. *J A M A* 126 873-877, 1944
- 57 Jones, M, and Mellersh, V Comparison of exercise response in anxiety states and normal controls. *Psychosomat Med* 8 180-187, 1946
- 58 Cohen, M E, Johnson, R E, Cobb, S, Chapman, W P and White, P D Studies of work and discomfort in patients with neurocirculatory asthma. *J Clin Investigation* 23 934, 1944
- 59 Watkins, A L, Cobb, S, Finesinger, J E, Brazier, M A B, Shands, H C, and Pincus, G Psychiatric and physiologic studies on fatigue: preliminary report. *Arch Phys Med* (in press)
- 60 Ray, G B, Johnson, J R, and Ray, L H Change in reduction time of blood after breath holding as criterion of physiological fitness. *Am J Physiol* 147 636-646, 1946
- 61 Harvey, V K, and Luongo, E P Physical capacity for work. Principles of industrial physiology and psychology related to evaluation of working capacity of physically impaired. *Occup Med* 1 1-47, 1946
- 62 Griffiths, H E Functional job analysis. *Brit J Phys Med* 9 43-46, 1946
- 63 Van Amberg, R J Clinical test for effort tolerance. *Occup Med* 1 363-375, 1946
- 64 Offner, F Stimulation with minimum power. *J Neurophysiol* 9 387-390, 1946
- 65 Fischer, E, and Ramsey, V W Effect of daily electrical stimulation of normal and denervated muscles upon their protein content and upon some of physicochemical properties of protein. *Am J Physiol* 145 583-586, 1946
- 66 Idem Changes in protein content and in some physico-chemical properties of protein during muscular atrophies of various types. *Am J Physiol* 145 571-582, 1946
- 67 Kosman, A J, Osborne, S L, and Ivy, A C Effect of electrical stimulation upon course of atrophy and recovery of gastrocnemius of rat. *Am J Physiol* 145 447-451, 1946
- 68 Young, J Z Effects of use and disuse on nerve and muscle. *Lancet* 2 109-113, 1946
- 69 Suskind, M I, Hajek, N M, and Hines, H M Effects of massage on denervated skeletal muscle. *Arch Phys Med* 27 133-135, 1946

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

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CASE 33211

PRESENTATION OF CASE

A forty-six-year-old restaurant manager entered the hospital because of dyspnea and swelling of the ankles.

The patient had been well until two and a half years before admission, when he suffered from the gradual onset of marked dyspnea, moderate ankle edema, easy fatigability, orthopnea and attacks of nocturnal dyspnea. After six months he consulted a physician, and under bed rest, digitalis and intravenous diuretics the symptoms subsided. Five weeks later he resumed work but continued to have moderate dyspnea without ankle swelling until four months before entry, when all the former symptoms gradually returned. He was, however, able to continue his job until a month before admission, when the symptoms became so severe as to force him to bed. Brief attacks of nocturnal breathlessness occurred almost every night. The edema failed to disappear on bed rest, but never extended above the ankles. The patient became extremely anorexic, was unable to sleep well and needed three or four pillows. Over a two-year period there had been occasional episodes of coughing productive of yellow mucus with moderate exacerbation in the last month. There

was no history suggesting rheumatic fever, syphilis or hypertension.

Physical examination disclosed a patient who was sitting in bed in slight respiratory distress and coughing frequently and forcefully. The lungs were resonant and clear. The cardiac border extended to the anterior axillary line in the seventh intercostal space. Thrills were palpable at the apex and in the third and fourth interspace to the left and right of the sternum. A high-pitched Grade IV systolic murmur, followed by a low, rumbling diastolic murmur, was audible at the apex. Along the left sternal border there was a harsh Grade IV systolic and loud, high-pitched diastolic murmur. The rhythm was regular, and the rate 75 per minute. The liver edge extended 3 cm below the right costal margin and was tender and firm. The spleen was not palpable. There was moderate edema over the lower portion of the back and marked edema of the legs. The feet were warm.

The temperature was 98°F, the pulse 76, and the respirations 16. The blood pressure was 106 systolic, 80 diastolic.

Examination of the blood revealed a red-cell count of 4,300,000, with a hemoglobin of 13.8 gm per 100 cc, and a white-cell count of 12,500, with 74 per cent neutrophils. The urine gave a ++ test for albumin, the sediment contained an occasional white cell only. The nonprotein nitrogen was 45 mg, the fasting blood sugar 95 mg and the total protein 5.4 gm per 100 cc.

Treatment consisted only of bed rest, mild sedation, ammonium chloride and continuance of digitalis. During the second night in the hospital the patient was unusually restless. The next morning he looked poorly, he was sweating profusely and felt weak. Physical examination revealed no change except that the pulse was totally irregular and the blood pressure was 112 systolic, 102 diastolic. Two or three minutes after being examined the patient

suddenly had a tonic convulsion and died. On application of a stethoscope to the chest within thirty seconds after the onset of the convulsion no heart sounds could be heard.

DIFFERENTIAL DIAGNOSIS

DR SYLVESTER MCGINN: It seems to me that the diagnosis in this case revolves around an interpretation of the thrills and the murmurs. As the heart sounds are recorded in this abstract considerable desirable information is lacking. For instance I should like to know about the pulmonic second sound and whether or not it was accentuated enough to suggest pulmonary regurgitation.

DR TRACY B. MALLORY: I carefully looked through the record for that information but could not find it.

DR MCGINN: I should like to know about the timing of the thrills.

DR MALLORY: Can you answer any of these questions, Dr. Bland?

DR EDWARD F. BLAND: No.

DR MCGINN: Cyanosis is not mentioned, I assume that it was not observed. A productive cough had been present for two years but there is no record of a sputum examination which I again assume was not done. The x-ray studies might be helpful, and the cardiologist finds some solace in electrocardiograms. I am sure that electrocardiograms were not taken since we are not given that information. I should like to know the albumin-globulin ratio. Occasionally, with edema of the lower legs, lipoid nephrosis is present. In this case the urine showed a ++ test for albumin, but I think that we have other information that will probably account for the diagnosis without the several things that I have made reference to. It is apparent that left and right ventricular failure was present, the cardiac asthma and nocturnal dyspnea being indicative of weakness of the left side of the heart and the engorged liver and the edema being indicative of right heart failure. Constrictive pericarditis could give the appearance of right ventricular failure, but in that condition the patient is usually not orthopneic, on that basis I believe that this diagnosis can be excluded.

Thrills may be due to valvular heart disease or congenital lesions and sometimes occur with acute dilatation of the heart. Acute dilatation can be due to acute rheumatic myocarditis or adhesive pericarditis or may represent the dilatation that is terminal in a large hypertrophied heart. It is difficult to believe that it was present in this case with a pulse rate of only 75. The temperature was normal. I think that there was something beyond acute dilatation to explain the thrills.

There are several kinds of systolic thrills, but when a thrill is maximal in the third or fourth interspaces, one thinks first of a congenital anomaly such as Roger's disease or an interventricular septal defect, in such cases, however, the heart is usually small.

The heart in this case was large. The location of the thrill could go with a pulmonary stenosis. In pulmonary stenosis the thrill is generally felt in the second left interspace and in most cases of pulmonary stenosis cyanosis is such a marked feature that it is included in the record of the examination. The thrill of aortic stenosis in the early stage is located in the second right interspace as a rule, but as cardiac hypertrophy progresses it is possible for the thrill and the murmur to be displaced downward even to the third and fourth interspaces. The thrills in this case were not timed but the most frequent apical thrill is the diastolic thrill of mitral stenosis. Occasionally diastolic thrills occur at the left sternal border, but if so they are due to rupture of the aortic-valve cusps, a rare condition. The description of the murmurs at the apex in this case report signifies mitral regurgitation and mitral stenosis and I think that they must be accepted as such. We must account for systolic and diastolic murmurs at the left sternal border which might have been due either to pulmonary stenosis with regurgitation or to aortic stenosis with regurgitation, probably the latter. There is no indication that the systolic murmur was transmitted to the neck. I think that that finding would tend to clinch this diagnosis. Left ventricular failure is evidenced by the history of cardiac asthma and right ventricular failure by liver enlargement. The statement that the cardiac border was in the seventh interspace at the anterior axillary line indicates an extremely large heart. Death was apparently primarily cardiac. I do not believe that it was embolic. The heart sounds were inaudible when the patient was examined within thirty seconds after death. The arrhythmia that preceded the exitus was probably due to coronary insufficiency and ventricular fibrillation. The possibility of a pulmonary embolus in congestive heart failure is great. It is my impression that the outstanding lesion in this case was aortic stenosis of high grade and with calcification of the valve. The location of the murmur and the thrill bears this out, as does the small pulse pressure, the low blood pressure and the regular rhythm. Patients with mitral stenosis in congestive failure are usually fibrillating unless some other lesion is predominating.

Finally we must consider the mode of death. Patients with aortic stenosis often die suddenly. I do not know whether or not there was interference with the coronary circulation.

CLINICAL DIAGNOSES

Rheumatic heart disease
Aortic stenosis and regurgitation
Mitral regurgitation and () stenosis
Congestive failure

DR MCGINN'S DIAGNOSES

Rheumatic heart disease
Aortic stenosis and regurgitation with calcification

Mitral stenosis and regurgitation
 Cardiac hypertrophy
 Congestive failure, left and right ventricles

ANATOMICAL DIAGNOSES

Calcareous aortic stenosis
Congenital bicuspid aortic valve
Hypertrophy of left ventricle, marked
Deviation of interventricular septum ? Bernheim syndrome
 Mural thrombi, left and right auricles
 Pulmonary embolus, small, left upper lobe
 Chronic passive congestion, lungs, liver and spleen
 Pancreatitis, chronic, of moderate severity

PATHOLOGICAL DISCUSSION

DR MALLORY Autopsy showed an extremely hypertrophied heart, the cause of which was an obviously stenotic aortic valve (Fig 1) It appeared to have only two cusps, both of which were mas-

Some difference of opinion was expressed regarding the mitral valve I thought that it was normal, without evidence of rheumatic heart disease The coronary arteries showed minimal atheromatosis The left ventricle was particularly hypertrophied (Fig 2), and the right ventricle was reduced to a rather narrow slit This suggested the possibility of a Bernheim syndrome, if one believes in such a thing, and I should like to raise that point for discussion To those not familiar with the hypothesis, Bernheim¹ suggested many years ago that in certain cases of massive dilatation or hypertrophy of the left ventricle, deviation of the septum into the right ventricle produced sufficient narrowing of the right ventricle so that it was unable to fill properly with blood and failure of the right side of the heart occurred secondary to left ventricular hypertrophy

Have you any comment, Dr Bland?

DR BLAND I have never recognized this syndrome clinically Once or twice a year someone from the



FIGURE 1 Photograph of the Aortic Valve

sively calcified, and there were great warty excrescences of calcium in the sinuses of Valsalva Each of these cusps appeared considerably larger than a normal cusp On one side I think that a ridge could be made out in the middle of the cusp, such as that seen in congenital fusion of the aortic valve It is my impression that a large proportion of these calcareous aortic stenoses develop on the basis of congenital bicuspid valves, and this case suggests that etiology

DR WALTER BAUER What do you mean by a large percentage — 20 or 80 per cent?

DR MALLORY Eighty per cent

Pathology Department presents us with a possible example post mortem It is an interesting concept It implies not exactly right-sided heart failure but rather an inability of the blood to get into the right ventricle In 1945, 3 cases that clinically fit in more or less with this concept were described² The patients were said to have had right-sided heart failure, swelling and edema, without previous pulmonary congestion (left-sided heart failure), and at post mortem the sections were similar to the one that Dr Mallory has just demonstrated

DR MALLORY Those who believe in the syndrome consider the diagnosis to require evidence of right-

ded heart failure before evidence of left-sided heart failure. In most published cases evidence of such a sequence is sketchy, as in the case under discussion. This man had paroxysmal dyspnea, probably due to left ventricular failure at an early stage in the symptoms.

DR. BLAND: I wonder if that concept need be true. It takes time for the left ventricle to encroach by hypertrophy or dilatation into the right ventricular cavity. May it not be failing at that time, whereas later on it actually obstructs the inflow into the right ventricle and the signs of right-sided heart failure intervene?

DR. MCGINN: This is an early age for occurrence and an unusual period for a patient with aortic

DR. MALLORY: No anatomic immediate cause of death was found. I think that one must assume that it was due to ventricular fibrillation.

REFERENCES

1. Bernheim: De l'asthénie veineuse dans l'hypertrophie du cœur gauche par sténose concomitante du ventricule droit. *Revue de médecine* 30: 744-501, 1910.
2. Russek, H. I., and Zohman, B. L.: Syndrome of Bernheim. *Am Heart J* 30: 427-441, 1945.

CASE 33212

PRESENTATION OF CASE

A fifty-eight-year-old Polish mill worker entered the hospital because of hematuria.

Ten months before admission there had been a single episode of painless massive hematuria. Three months later hematuria began intermittently, and gradually became more frequent and severer so that by the week before entry the patient was passing "jelly-like" urine. No symptoms attended this bleeding until two days before admission, when there was mild left-flank discomfort.

The patient had had a chronic cough for years, but there was no history of tuberculosis or other major illness.

Physical examination disclosed persistent moist rales at both lung bases. The heart and abdomen were normal. There was no costovertebral-angle tenderness. Rectal examination revealed the prostate to be enlarged two and a half times normal, soft, smooth and symmetrical, and a sessile mass, about 3 cm. in diameter, was palpated high in the posterior rectal wall. A cystoscope was passed easily. There was a long, worm-like clot lying unattached in the floor of the bladder. The mucosa was normal, and the capacity 300 cc. The trigone and ureteral orifices looked normal. Clear urine was ejected from the right ureter, none from the left. There was mild hypoplasia of the median and lateral lobes of the prostate, the prostatic urethra appeared normal. Catheters were passed to 28 cm. on both sides, a slight obstruction being felt at 25 cm. on the left. Bloody fluid was aspirated from the left ureter, although there seemed to be no actual production of urine on that side. A smear of this fluid prepared according to the Papanicolaou technic showed tumor cells. Indigo-carmin appeared on the right two and a half minutes after injection, none was seen on the left.

The temperature was 99°F, the pulse 88, and the respirations 22. The blood pressure was 180 systolic, 100 diastolic.

Examination of the blood revealed a red-cell count of 4,650,000, with a hemoglobin of 85 per cent, and a white-cell count of 11,200. The urine had a specific gravity of 1.014 and gave a +++ test for albumin. Urine culture revealed no growth. The sediment contained innumerable red cells. The total protein, nonprotein nitrogen, carbon dioxide and chloride were normal.



FIGURE 2. Photograph of a Cross Section of the Heart

stenosis to survive in congestive failure unless explained by a damaged myocardium or by the Bernheim theory.

DR. MALLORY: The patient died at an early age for calcareous stenosis — fifteen years younger than the average.

DR. MCGINN: When congestive failure appears with aortic stenosis there is usually a downhill course over a period of seven or eight months. I believe that this case was complicated either by myocardial changes or by a Bernheim syndrome.

DR. BAUER: This case may have been the exception.

DR. MALLORY: Yes.

DR. MCGINN: In answer to the question about the mitral murmurs, it is possible for a dilated heart to give the findings of mitral stenosis with a typical murmur and thrill in the presence of a normal valve. It is interesting that in this case the maximal location of the aortic-valve murmur and thrill was in the third and fourth interspaces.

A PHYSICIAN: Have you seen any cases of the presystolic crescendo that turned out to have a normal mitral valve?

DR. MCGINN: I recall a case that seemed to be so typical that a valvulotomy was done.

A PHYSICIAN: What do you consider the cause of death in the case under discussion?

Mitral stenosis and regurgitation
 Cardiac hypertrophy
 Congestive failure, left and right ventricles

ANATOMICAL DIAGNOSES

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DR TRACY B. MALLORY Dr Chute will you tell us the operative findings?

DR RICHARD CHUTE I helped Dr Rogers, the resident do the operation. The lesion turned out to be a papillary tumor of the kidney, which was removed by transperitoneal nephrectomy. The kidney was approximately normal in size. There was papillomatosis of the renal pelvis, which was much more marked in the upper pole than in the lower pole. The upper calyces were entirely filled with tumor, whereas in the lower ones there was a considerable amount of space that the retrograde dye could not enter.

DR COLBY What was the preoperative diagnosis?

DR CHUTE Tumor of the kidney.

A PHYSICIAN Was there any drop in blood pressure after operation?

DR MALLORY Nothing to suggest shock.

A PHYSICIAN Was not the diagnosis of tumor made on interpretation of the pyelogram?

DR COLBY I think that in this case we paid a good deal of attention to the tumor cells. Is that true, Dr Chute?

DR CHUTE The pyelogram offered one bit of contributory evidence but we were not swayed by that.

DR COLBY I was interested in Dr Dean's remark regarding Dr Papanicolaou's technic because we are now going through the throes of trying to evaluate the smear diagnosis of carcinoma in cases such as this. We are not yet certain about this test. In one case we got a positive report of tumor cells, and since there was a definite renal defect on x-ray examination, the kidney was removed, but no tumor was present anywhere in the kidney. That set us back on our heels a good deal. The disturbing thing was that the slide that contained the tumor cells was broken, so that we were unable to check it. We believe that the presence of tumor cells in the urine is not sufficient justification for removing a kidney. This test is still in the experimental stage, and we do not wish to decry the procedure on one unfortunate experience. Everyone, including the X-ray Department, thought that we were justified in operating on the patient regardless of the presence or absence of the tumor cells in the urine.

DR DEAN There are two conditions that we know of in which tumor-like cells can be found and one would not wish to remove the kidney. One is adenoma of an exceedingly low grade of malignancy. The other is ureteritis cystica. The cells from the surfaces of the small cysts look like those of a papilloma.

DR DAVID W. WILLIAMS In our experience in a series of 100 consecutive cases there were positive reports in 8, and 7 of these patients were proved to have tumors. One out of every 8 in other words, is an error.

DR MALLORY The same diagnostic problem of the value of smear diagnosis of cancer, of course, holds for cancer of the female genital tract and of the lung. There are cases in which it is impossible to obtain a biopsy specimen and in which smear examination has led to a positive diagnosis. For instance cancer of the fallopian tube has been correctly diagnosed on smear. In the lung it is not uncommon to have a tumor so far out in the periphery that it is impossible to reach it with a bronchoscope. We believe that a positive smear constitutes important evidence. We are still conservative, however, in accepting it without other support, and if there is any chance of confirming the diagnosis with biopsy of the old-fashioned sort, we always do it.

A PHYSICIAN How much better are aspiration biopsies than the Papanicolaou technic?

DR MALLORY That depends entirely on who takes the biopsy. There is in my experience about one surgeon in twenty who can take satisfactory aspiration biopsies. The rest are not worth looking at. It seems like a simple technic, but most people are not successful in providing anything on which I can make a diagnosis.

A PHYSICIAN Are the successful surgeons consistent?

DR MALLORY Yes, most of them have learned the technic elsewhere — in Stockholm or at the Memorial Hospital in New York.

CLINICAL DIAGNOSIS

Renal tumor

DR DEAN'S DIAGNOSIS

Tumor of upper pole of left kidney

ANATOMICAL DIAGNOSIS

Papillary carcinoma of left renal pelvis

PATHOLOGICAL DISCUSSION

DR MALLORY The real question came up in the later handling of this patient with a papillary tumor of the renal pelvis. One knows the possibility of recurrence of such a tumor, whether by implantation or not farther down in the ureter and sometimes in the bladder. This man had a simultaneous carcinoma of the rectum, and he eventually went through three operations.

DR COLBY One question that came up was whether it was advisable to remove the entire ureter, since the patient had another cancer.

DR MALLORY I think that the cancer of the rectum was far more important than the possibility of cancer of the ureter.

A PHYSICIAN It is easy to take out the stump of the ureter when the rectum is removed.

DR MALLORY I should think that would be the best procedure in such circumstances.

An intravenous pyelogram showed normal function on the right, but none on the left. A retrograde pyelogram demonstrated markedly dilated calyces in the lower portion of the left kidney, no calyces filled in the upper portion. The ureter was not outlined, but the ureteropelvic insertion appeared to be low. X-ray films of the skull and spine showed no evidence of tumor. Biopsy of the rectal mass showed adenocarcinoma.

A renal operation was performed on the sixth hospital day.

DIFFERENTIAL DIAGNOSIS

DR ARCHIE L. DEAN* The history suggests organic disease somewhere in the genitourinary organs, and the painless massive hematuria suggests that it came from one of the kidneys. "Massive" seems to be the term to use in this case. I think that the term "total hematuria" is a good one too, indicating that the blood is diffused equally throughout all the urine, in contradistinction to initial or terminal hematuria. That is one of the characteristics of bleeding from the kidney. It should be emphasized that the hematuria, no matter what the cause, was always intermittent in this case.

I assume that the sessile mass in the wall of the rectum represented a carcinoma of the rectum.

"There was a long, worm-like clot lying unattached in the floor of the bladder." That also helps to localize the source of the bleeding in one of the kidneys, because not infrequently if the kidney bleeding is sufficiently severe so that clots form, a perfect cast of the ureter is passed.

"Clear urine was ejected from the right ureter, none from the left." This was at a time of bleeding so that we are assisted to a certain extent in localizing this hemorrhage in the left kidney or ureter.

After referring several hundreds of specimens to Dr. Papanicolaou while he was developing his technic, I can state that a definitely positive diagnosis is of considerable clinical significance. By the use of this technic, however, one would not expect to be able to differentiate a tumor of the renal pelvis from a tumor of the renal parenchyma that had ulcerated into the pelvis.

"Indigo-carmin appeared on the right two and a half minutes after injection, none was seen on the left." That may or may not have significance in relation to the hypertension, on the basis of obstruction of the vascular system of the left kidney.

The x-ray appearance could have been due to a tumor of the parenchyma, with obliteration of the upper calyces. It could also have been caused by tumor of the pelvis. It is less likely that it was due merely to a clot.

The ureter was not outlined, but the ureteropelvic insertion appeared to be low — there may be significance in this, but I do not believe that

There is no mention of a film of the chest, I should like to see one.

Biopsy of the rectal mass showed adenocarcinoma. Since the most frequent type of tumor of the renal parenchyma is an adenocarcinoma, one wonders if there was an association. I think that such an association is extremely rare, although multiple tumors are quite common. But either a primary adenocarcinoma of the kidney giving rise to metastases in the rectum or a rectal tumor involving the kidney is too rare to be considered seriously.

DR LAURENCE L. ROBBINS A film of the chest was taken, and so far as I can see, the chest is entirely normal. There is no evidence of tumor. The changes in the heart and aorta are what one would expect in a man of this age. The lungs are essentially clear.

The pyelograms are essentially as described in the protocol. In the intravenous pyelogram there is no evidence of function on the left side over a relatively limited period. The right urinary passages are, so far as I can see, normal. This is a film of a retrograde pyelogram. On the left side we see filling of the inferior calyces, which are dilated, with some irregularity along this area. The ureteropelvic insertion appears to be lower than is usual. At no time do we see a good kidney outline, other than the lower pole, on the left side. This film suggests that the upper pole is somewhat widened at this point, but I do not believe that the film is sufficiently detailed to be certain.

DR DEAN This appears to be a pyelogram of a tumor of the upper pole of the kidney, obliterating the upper calyces.

A PHYSICIAN Could it not be a double kidney?

DR DEAN It could be, although it does not look just right for that.

Another point is that there is usually some degree of function in a kidney that has a tumor limited to the upper pole. The lack of function is something that I have not been able to understand. I am uncertain because the picture is not clear cut. But on the basis of the findings, the best I can suggest is a tumor of the upper pole of the left kidney.

A PHYSICIAN I should like to ask if Dr. Robbins can recognize the outline of a mass on the left. From where I sit I can see a definite shadow.

DR ROBBINS So far as I can tell the mass to which you refer is produced simply by the colon swinging around in this manner. This other mass, of course, is fluid in the fundus of the stomach, which disappears as soon as the patient is turned over on the abdomen, when it is replaced with air. The thing that is bothersome is that it is not possible to see a definite mass in the region of the upper pole of the kidney.

A PHYSICIAN Do we have any information about the differential count? The white-cell count was 11,200, but no differential is given.

DR FLETCHER H. COLBY It was normal.

BAULEY
20 or 80
Cornell

result from environmental circumstances — from better standards of living and, in particular, from better nutrition

The converse has been seen in war-stricken countries, where mass malnutrition, amounting in places to mass starvation, has seriously stunted the growth of a generation of children. It is in an attempt to evaluate the factors involved that Talbot and his associates have made the studies reported elsewhere in this issue of the *Journal*.

These investigators found that, of a group of over a hundred abnormally short children from two and a half to fifteen years of age, 51 per cent showed no physical disturbance and no hereditary factor to account for the stuntedness. The majority of the patients had presented difficult feeding problems for most of their lives, although the average protein intake, if properly assimilated, was considered to be adequate in all for normal growth. The conclusion was reached that the caloric intake in these cases was more important than the protein itself, because in the absence of sufficient calories from other foods, the protein intake and probably some part of the body protein as well were called on to produce energy.

Attempts to improve the situation by an increased diet were usually unrewarded by any co-operative response on the part of the patients, and further analysis of the group showed that in the majority one or more of certain untoward factors were present. These consisted of mental deficiency or an emotional reaction to poor environmental factors on the part of the patients, of poor family economic situations and of emotional instability, delinquency or psychosis on the part of the mothers.

Correction of the emotional difficulties usually resulted in improved appetite and a gain in weight, but not always in a resumption of growth.

The conclusions may be drawn that growth failure is the indirect result only of malnutrition and that it follows directly from a lack of pituitary growth hormone, this lack being due to the poor nutrition. Such conclusions are strengthened by the fact that improved growth may not result from the acceptance of an adequate diet but does result when methyl testosterone is added to the diet.

MASSACHUSETTS MEDICAL SOCIETY

DEATH

TIGHE — Michael A. Tighe, M.D., of Lowell, died April 8. He was in his sixty-sixth year.

Dr. Tighe received his degree from Harvard Medical School in 1908. He was formerly president of the Middlesex North District Medical Society, and was secretary of the Massachusetts Medical Society. He was a fellow of the American College of Surgeons, New England Obstetrical and Gynecological Society, and American Medical Association.

He is survived by his widow, three sons, a daughter, five grandchildren and two sisters.

MISCELLANY

METOPON HYDROCHLORIDE

In 1929, with the funds provided by the Rockefeller Foundation, the National Research Council, through the Committee on Drug Addiction, undertook a co-ordinated program to study drug addiction and search for a nonaddicting analgesic comparable to morphine. The principal participating organizations were the University of Virginia, the University of Michigan, the United States Public Health Service, the Treasury Department's Bureau of Narcotics and the Massachusetts Department of Public Health, which brought together chemical, pharmacologic and clinical facilities for the purpose of the study. Metopon (methyl dihydromorphine hydrochloride) is one of the many compounds made and studied in this co-ordinated effort.

Metopon is a morphine derivative. Pharmacologically, it is qualitatively like morphine even to the properties of tolerance and addiction liability. Chemically, Metopon differs from morphine in three particulars — one double bond of the phenanthrene nucleus has been reduced by hydrogenation, the alcoholic hydroxyl has been replaced by oxygen and a new substituent, a methyl group, has been attached to the phenanthrene nucleus. Studies made thus far indicate that, pharmacologically, Metopon differs from morphine quantitatively in all its important actions — its analgesic effectiveness is at least double and its duration of action is about equal to that of morphine, it is nearly devoid of emetic action, tolerance to it appears to develop more slowly and to disappear more quickly and physical dependence builds up more slowly than with morphine, therapeutic analgesic doses produce little or no respiratory depression and much less mental dullness than do those of morphine, and it is relatively effective by oral administration.

In addition to animal experiments these differences have been established by extensive employment of the drug in two types of patients — those addicted to morphine and others, such as patients in the terminal stages of cancer, needing prolonged pain relief but without previous opiate experience. In morphine addicts, Metopon appears only partially to prevent the impending signs of physical and psychological dependence. In terminal cancer, administered orally, it gives adequate pain relief with little mental dulling, without nausea or vomiting and with slow development of tolerance and dependence. The latter properties place Metopon in a class by itself for the treatment of the chronic suffering of cancer, and it is for that purpose exclusively that it is being manufactured and marketed.

The capsules are put up in bottles of 100, and each capsule contains 50 mg. of Metopon hydrochloride. They can be obtained by physicians only from Sharp and Dohme or Parke, Davis and Company, on a regular official narcotic order form, which must be accompanied by a signed statement supplying information concerning the number of patients to be treated and the diagnosis on each. The drug will be distributed only for the purpose of oral administration for the relief of chronic pain in cancer cases.

The dose of Metopon hydrochloride is 60 to 90 mg. (two or three capsules) to be repeated only on recurrence of pain, avoiding regular by-the-clock administration. As with morphine, it is most desirable to keep the dose at the lowest level compatible with adequate relief of pain. Therefore, administration should be started with two capsules per dose, increasing to three only if the analgesic effect is insufficient.

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

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MATERIAL should be received not later than noon on Thursday, three weeks before date of publication

THE JOURNAL does not hold itself responsible for statements made by any contributor

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts

NEW YORK ACADEMY OF MEDICINE

THE autumn that saw the first public demonstration of ether as an anesthetic also witnessed another event less spectacular in its nature and less far-reaching in its influence, but still of continuing importance to the progress of medicine. This event was the annual meeting, at Peletier's Restaurant, on Broadway, New York City, of the Society for the Relief of Widows and Orphans of Medical Men. The importance of this particular meeting, a century ago, was that from it came the preliminary plans for the establishment of the New York Academy of Medicine.

The original function of the Academy, according to its story as told by Dr. Howard A. Rusk, in the March 9 issue of the *New York Times*, was "to promote the honor, dignity, the respectability and the usefulness of the medical profession." That

function has not changed, and the distinction with which it has been discharged has increased as the years have rolled on, even until this, the year when its centennial celebration has recently been observed.

Important among the various functions of the Academy has been the maintenance of its library, coeval with the Academy itself, and now numbering 225,000 volumes, a library second in size only to the Army Medical Library in Washington. The Academy has also put on foot various studies contributing to the public health and to the practice of medicine, under its auspices are conducted public lectures on health and disease, similar to those sponsored in this city by the Harvard Medical School.

Various associations brought deliberately into being for the unselfish motive of improving the welfare of mankind have had long and inspiring histories. Such organizations have been the English and Scottish Royal Colleges of Physicians and Surgeons, dating back to the sixteenth century, and their American counterparts, as well as the Royal Society of London — the "Invisible College" — that rose, with others, in the seventeenth century. There have been many such associations, first and last, for the promotion of science in general and a better understanding of disease in particular, for "where there is love of man there is love of the art."

There is, curiously, no similar organization in New England, although the various functions of an academy are adequately carried on by the state medical societies, the medical schools and, notably, the Boston Medical Library, fellowship in which carries with it a dignity and an intellectual prestige that still have their value.

MALNUTRITION AND GROWTH

CERTAIN phenomena that have been observed in relation to growth in the human species deserve our attention. In a matter of generations, stature and general development have improved to a degree that can almost be measured in inches. This change is so general and has been so rapid that it cannot be attributed to any evolutionary deviation, heredity may play a part in it, but it must in the main

result from environmental circumstances — from better standards of living and, in particular, from better nutrition

The converse has been seen in war-stricken countries, where mass malnutrition, amounting in places to mass starvation, has seriously stunted the growth of a generation of children. It is in an attempt to evaluate the factors involved that Talbot and his associates have made the studies reported elsewhere in this issue of the *Journal*.

These investigators found that, of a group of over a hundred abnormally short children from two and a half to fifteen years of age, 51 per cent showed no physical disturbance and no hereditary factor to account for the stuntedness. The majority of the patients had presented difficult feeding problems for most of their lives, although the average protein intake, if properly assimilated, was considered to be adequate in all for normal growth. The conclusion was reached that the caloric intake in these cases was more important than the protein itself, because in the absence of sufficient calories from other foods, the protein intake and probably some part of the body protein as well were called on to produce energy.

Attempts to improve the situation by an increased diet were usually unrewarded by any co-operative response on the part of the patients and further analysis of the group showed that in the majority one or more of certain untoward factors were present. These consisted of mental deficiency or an emotional reaction to poor environmental factors on the part of the patients, of poor family economic situations and of emotional instability, delinquency or psychosis on the part of the mothers.

Correction of the emotional difficulties usually resulted in improved appetite and a gain in weight, but not always in a resumption of growth.

The conclusions may be drawn that growth failure is the indirect result only of malnutrition and that it follows directly from a lack of pituitary growth hormone, this lack being due to the poor nutrition. Such conclusions are strengthened by the fact that improved growth may not result from the acceptance of an adequate diet but does result when methyl testosterone is added to the diet.

MASSACHUSETTS MEDICAL SOCIETY

DEATH

TIGHE — Michael A. Tighe, M.D., of Lowell, died April 8. He was in his sixty-sixth year.

Dr. Tighe received his degree from Harvard Medical School in 1908. He was formerly president of the Middlesex North District Medical Society, and was secretary of the Massachusetts Medical Society. He was a fellow of the American College of Surgeons, New England Obstetrical and Gynecological Society and American Medical Association.

He is survived by his widow, three sons, a daughter, five grandchildren and two sisters.

MISCELLANY

METOPON HYDROCHLORIDE

In 1929, with the funds provided by the Rockefeller Foundation, the National Research Council, through the Committee on Drug Addiction, undertook a co-ordinated program to study drug addiction and search for a nonaddicting analgesic comparable to morphine. The principal participating organizations were the University of Virginia, the University of Michigan, the United States Public Health Service, the Treasury Department's Bureau of Narcotics and the Massachusetts Department of Public Health, which brought together chemical, pharmacologic and clinical facilities for the purpose of the study. Metopon (methyldihydromorphine hydrochloride) is one of the many compounds made and studied in this co-ordinated effort.

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In addition to animal experiments these differences have been established by extensive employment of the drug in two types of patients — those addicted to morphine and others, such as patients in the terminal stages of cancer, needing prolonged pain relief but without previous opiate experience. In morphine addicts, Metopon appears only partially to prevent the impending signs of physical and psychical dependence. In terminal cancer, administered orally, it gives adequate pain relief with little mental dulling, without nausea or vomiting and with slow development of tolerance and dependence. The latter properties place Metopon in a class by itself for the treatment of the chronic suffering of cancer, and it is for that purpose exclusively that it is being manufactured and marketed.

The capsules are put up in bottles of 100, and each capsule contains 50 mg. of Metopon hydrochloride. They can be obtained by physicians only from Sharp and Dohme or Parke, Davis and Company, on a regular official narcotic order form, which must be accompanied by a signed statement supplying information concerning the number of patients to be treated and the diagnosis on each. The drug will be distributed only for the purpose of oral administration for the relief of chronic pain in cancer cases.

The dose of Metopon hydrochloride is 60 to 90 mg. (two or three capsules), to be repeated only on recurrence of pain, avoiding regular by-the-clock administration. As with morphine, it is most desirable to keep the dose at the lowest level compatible with adequate relief of pain. Therefore, administration should be started with two capsules per dose, increasing to three only if the analgesic effect is insufficient.

Tolerance to any narcotic drug develops more rapidly with excessive dosage and under regular by-the-clock administration. Also as a rule, the pain of cancer varies widely in intensity from time to time. Pain, therefore, should be the only guide to the time of administration and the dosage level. Tolerance to Metopon hydrochloride develops slowly. It can be delayed or interrupted entirely by withholding the drug occasionally for twelve hours or for as much of that period as the incidence of pain will permit.

To each physician will be sent a record card for each patient to whom Metopon hydrochloride is to be administered. He will be requested to fill out these cards and to return them in the addressed return envelope. He must furnish this record of his patient and his use of Metopon hydrochloride if he wishes to repeat his order of the drug. The principal object of this detailed report is to check the satisfactoriness of the use of Metopon hydrochloride in general practice. The physician's co-operation in making it as complete as possible is earnestly solicited.

The limited use of Metopon hydrochloride as described above has been recommended by the Committee on Drug Addiction, National Research Council, and the committee, with the co-operation of the American Cancer Society, will supervise the distribution of the drug. The committee is composed of Dr. William Charles White, chairman, Washington, D. C., H. J. Anslinger, Commissioner of Narcotics, United States Treasury Department, Washington, D. C., Lyndon F. Small, National Institute of Health, Washington, D. C., and Dr. Nathan B. Eddy, National Institute of Health, Washington, D. C. Queries and comments on Metopon may be directed to Dr. Eddy, who will answer them for the committee.

BIBLIOGRAPHY

- Eddy, N. B. Search for more effective morphine like alkaloids. *Am J M Sc* 197 464-479 1939
- Himmelsbach, C. K. Studies of certain addiction characteristics of (a) dihydro-morphine ('paramorphan') (b) dihydrodesoxy-morphine D ('desomorphine') (c) dihydrodesoxy-codeine D ('desocodeine') and (d) methyl-dihydro-morphinone ('metopon'). *J Pharmacol & Exper Therap* 67 239 249 1939
- Lee, L. E. Jr. Medication in control of pain in terminal cancer with reference to study of newer synthetic analgesics. *J A M A* 116 216-220 1941
- Idem. Studies of morphine, codeine and their derivatives. XVI. Clinical studies of morphine, methyl-dihydro-morphinone (metopon) and dihydro-desoxy-morphine D (desomorphine). *J Pharmacol & Exper Therap* 75 161 173 1942
- Small, L. and Fitch, H. M. U. S. Patent No. 2178 010 October 31 1939
- Small, L., Fitch, H. M. and Smith, W. E. Addition of organomagnesium halides to pseudocodeine types. II. Preparation of nuclear alkylated morphine derivatives. *J Am Chem Soc* 58 1457 1936
- Small, L., Turnbull, S. G. and Fitch, H. M. Addition of organomagnesium halides to pseudocodeine types. IV. Nuclear substituted morphine derivatives. *J Org Chem* 3 204 1938

CORRESPONDENCE

BASIS OF STUDENT HEALTH SERVICES

To the Editor: In view of the fact that there has been in the past and will be in the future considerable discussion between the relative advantages of a compulsory health-insurance plan and the development of medical-care programs on a voluntary prepaid basis, I think that the editorial "The Third National Conference on Health in Colleges" in the April 19 issue of the *Journal of the American Medical Association* is of interest. This editorial speaks of the organization of student health services on the basis of voluntary prepaid medical-care and hospital insurance. It is common knowledge, however, that at the present time many educational institutions, such as Harvard University, have a well organized medical-care program on a compulsory health-insurance basis. I am wondering whether the writer of the editorial would like to scrap the program that has been so successful at Harvard, replacing it with a voluntary insurance program.

CHANNING FROTHINGHAM, M.D.

101 Bay State Road
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BOOK REVIEWS

Pneumoperitoneum Treatment. By Andrew L. Banyai, M.D. 8°, cloth, 376 pp., with 74 illustrations and 16 tables. St. Louis: C. V. Mosby Company, 1946. \$6.50.

This book represents a compilation of practically all the literature on the subject of artificial pneumoperitoneum therapy, as well as an evaluation by the author, who has had extensive personal experience as a pioneer in this field. The book does not confine itself to pneumoperitoneum therapy in the narrow sense. It embraces the entire gamut of phthisiotherapy, as well as the many allied chest conditions, and appraises the place of this treatment in the entire scheme of general treatment. The physiology and the physiologic pathology of various chest and abdominal conditions, both tuberculous and nontuberculous, are well considered.

Although artificial pneumoperitoneum therapy is primarily employed in pulmonary tuberculosis, the author also discusses its use in such conditions as pulmonary abscess, bronchial asthma, bronchiectasis and pulmonary emphysema. In addition, he considers its role in abdominal adhesions, ulcerative colitis, intestinal and gastric bleeding and so forth. As yet, however, this form of therapy has not found the universal favor that artificial pneumothorax or thoracoplasty has. The adherents are vehement in their praise, but the greater portion of workers in the field of pulmonary tuberculosis have been lukewarm in their acceptance or have rejected the therapy entirely. This is easily explained by the chronicity, the protean nature and the many forms that such a disease as tuberculosis assumes. Nevertheless, regardless of the merits of artificial pneumoperitoneum therapy, the author has brought the extensive literature of the past ten to fifteen years up to date and has given the profession the benefit of his long and rich experience in this field. Whether this treatment is employed extensively or only occasionally, the book affords a ready reference and intelligent discussion of the many phases pertaining to the subject.

It is for this reason that the book should be read by all men interested in diseases of the chest. It should also find a place on the shelves of all medical libraries as a source of authoritative information.

Mother and Baby Care in Pictures. By Louise Zabriskie, R.N. Third edition, modernized. 8° cloth, 203 pp., with 229 illustrations and 7 tables. Philadelphia: J. B. Lippincott Company, 1946. \$2.00.

This new edition of a manual for mothers has been revised, and many additions and changes have been made in the text. Emphasis is placed on nutrition and the care of the baby. The mechanism of labor and the management of delivery in the hospital and the home are explained in great detail. The immediate care of the baby has been brought up to date, and the material on general care, habits and development during the first year has been entirely reorganized. The text is well organized and excellently illustrated. The plate on the male anatomy is superfluous and not pertinent and could have been omitted without detracting from the value of the book. The ring type of binding is not suitable for hard usage in the home. This manual should prove of value to all mothers and especially to expectant mothers.

Narco-Analysis: A new technique in short-cut psychotherapy. A comparison with other methods. And notes on the barbiturates. By J. Stephen Horsley. 12° cloth, 134 pp. New York and London: Oxford University Press, 1943. \$2.50.

This is the first American edition of this book, which was originally published in England in 1943. It concerns the technique and use of narcoanalysis in psychiatric illness. The author states that the theory of narcoanalysis involves both biochemical and psychodynamic concepts, the former being that persons who for a variety of reasons are sullen, reticent, inhibited or even mute may, during narcosis, converse spontaneously revealing anxiety conflicts or painful memories from which either consciously or unconsciously they seek refuge, whereas the latter incorporates the generally accepted views of conflict repression and amnesia with reference to their modification by hypnosis and analysis.

One chapter is devoted to a discussion of the barbiturates used in psychiatry, and the writer points out that since the number of barbiturates is increasing, he believes that personal

familiants with all forms is impossible, and he recommends a number that in his experience have proved successful.

The use of barbiturates is divided into three therapeutic classes: simple hypnotics, those providing a means of producing prolonged narcosis, and those affording a means of establishing contacts with previously reticent or inaccessible patients. In addition the chapter lists certain conditions that require special caution in their use. Old-age nephritis, liver disease, advanced cardiovascular disease, any tendency to respiratory spasm and toxemias are contraindications to the use of barbiturates.

The rationale of the procedure is explained by the statement that "narcosis is produced very slowly by the gradual administration of a suitable drug and during the stage of light narcosis, a true hypnotic state is induced by verbal suggestion, and the patient is then amenable to psychological analysis and synthesis." Under the influence of the barbiturates, because of the removal of inhibitions the latent or repressed conflict comes to the surface, and in a brief period the physician obtains information relevant to the patient's mental state that he could not have obtained in a month by ordinary means.

Following this the psychiatrist determines the salient factors responsible for the condition of the patient as well as the making of new associations to restore a normal attitude to reality. Two main indications are given for the use of narcoanalysis to overcome resistance and, in cases due to recent stress as a quick discovery of the principal emotional upset.

One chapter is devoted to a discussion of the employment of narcoanalysis in wartime. Two interesting reports are included on its use in the British Army and the Royal Navy. The chapters on abreaction and transference are instructive although the case reports are necessarily brief because of the small size of the book.

The author has presented his material in a clear and concise manner, the bibliography is extensive. The book is recommended as a valuable addition to the psychiatrist's library.

Sex, Marriage and Family. By Thurman B. Rice, M.D. 8th cloth, 272 pp. Philadelphia: J. B. Lippincott Company, 1946. \$2.50.

The author discusses in detail every aspect of marriage, from the basic sexual relation through all the conditions of married life, including psychological and economic factors and the physical, mental and emotional changes incidental to the change in family status, children and "in-laws." A special chapter is devoted to the problems of marriage in wartime, with emphasis on the status of the returned serviceman. The text is written in a bold, frank manner with a trace of flippancy, but on the whole, the proffered advice is sound and practical and should prove of value to interested persons of both sexes. It is to be deplored that the word "sex" is used as a synonym for sexual relation rather than in its correct sense.

Autopsy, Diagnosis and Technique. By Otto Saphir, M.D. With a foreword by Ludwig Hektoen, M.D. Second edition revised and enlarged. 12th, cloth, 405 pp., with 69 illustrations. New York: Paul B. Hoeber, Incorporated, 1946. \$5.00.

This practical manual of autopsy technique first published in 1937, has been enlarged by the addition of new material. The discussion of diseases of the breast has been greatly expanded in the interest of the general practitioner and student since the incidence of breast lesions is high, and there is a vital need of examining this region. New material has been added on accidental death, conditions peculiar to stillborn and newborn infants, nose and accessory sinuses, vitamin deficiencies and certain tropical diseases. Emphasis is placed on anatomically demonstrable lesions. The manual gives merely a diagnostic outline of the gross lesions generally found in structures and organs. Histopathologic lesions are not considered. Only one method of autopsy technique—a modified Robitansky procedure—is described.

The manual, which is written primarily for the student laboratory assistant and general practitioner, is well organized and should prove valuable to those interested in gross pathology.

Penicillin: Its practical application. Under the general editorship of Sir Alexander Fleming, M.B., B.S., F.R.C.P., F.R.C.S., F.R.S. 8th cloth, 50 pp., with 59 illustrations. Philadelphia: Blakiston Company, 1946. \$7.00.

The development of penicillin marks a dramatic episode in medical history.

It is appropriate that Sir Alexander Fleming, the discoverer, was invited by the Blakiston Company to edit "a series of independent contributions giving each author's views on the use of penicillin therapy in a disease or in infections of some region of the body" and that the collaborators he selected to take part in this undertaking were his English colleagues whose efforts combined to make the new antibiotic available for clinical use as promptly as possible.

The book is as British as John Bull. It was written by British authors and first printed in Great Britain and emphasizes the work on penicillin in England, although it by no means slight that of American investigators. And as is so often true in English medical books, the literary style of each chapter is uniformly excellent.

A delightful account is given of penicillin's discovery, its chemistry, manufacture, pharmacology and clinical use. The illustrations are interesting and indeed of historical importance since a picture is reproduced of the original culture plate on which the action of penicillin was observed. At the end of each chapter is a useful list of references leading to more detailed study of the subject under discussion. By way of conclusion, there is an admirable index.

On the whole, this is a noteworthy contribution that is almost faultless. The first printing of the first edition bids fair to rank as a medical classic. Any student or physician can read the monograph with benefit. It offers a restrained account of a most significant medical development, it gives sound advice regarding the proper management of many different clinical conditions, and it is a model of medical literature.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

X-Rays and Radium in the Treatment of Diseases of the Skin. By George M. MacKee, M.D., professor of clinical dermatology and director of Department of Dermatology (Skin and Cancer Unit), New York Post-Graduate Medical School and Hospital, Columbia University, and Anthony C. Cipollaro, M.D., assistant professor of dermatology and assistant director of Department of Dermatology (Skin and Cancer Unit), New York Post-Graduate Medical School and Hospital, Columbia University. With a contribution by Hamilton Montgomery, M.D., associate professor of dermatology, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. Fourth edition thoroughly revised. 8th cloth, 665 pp., with 321 illustrations. Philadelphia: Lea and Febiger, 1946. \$10.00.

Dr. MacKee and his collaborators have thoroughly revised this fourth edition of a standard work, first published in 1921 and revised from time to time. The authors have attempted to correlate the special knowledge of the dermatologist and the radiologist and to include the essential elements of physics and biology and seem to have succeeded in their objective. The first two chapters are devoted to a short and concise history of roentgen rays and radioactive elements. These are followed by chapters on physics and technique and finally on radiation of the skin in general and on the various diseases of the skin and tumors amenable to radiation therapy. The last chapter is on the medicolegal aspects of roentgen and radium therapy. A selective bibliography is appended to each chapter and a good index concludes the volume. The book is well printed in every way and a credit to the publisher. The work is recommended for all medical libraries and to physicians and others interested in the subject.

Progress in Neurology and Psychiatry An annual review Edited by E. A. Spiegel, M.D., professor and head of the Department of Experimental Neurology, Temple University School of Medicine 8°, cloth, 708 pp New York Grune and Stratton, 1946 \$8 00

This volume begins a new series of annual reviews in the fields of neurology and psychiatry in all their aspects. It is based primarily on the literature covering the period from December, 1944, to December, 1945. There are thirty-nine articles on pertinent subjects by recognized authorities and to each article is appended a complete list of references for the period covered. As an example, the review on pharmacology of the nervous system has a bibliography of seven hundred and twenty-eight articles. The objective of the work is to provide critical surveys of basic theoretical foundations, as well as the various clinical aspects of neurology and psychiatry. The book is well printed on a good soft paper. A slightly bolder type, however, would make for easier reading. The volume and its continuations are recommended for all medical libraries and should prove useful to all specialists in its fields.

Medical Services by Government Local, state and federal By Bernhard J. Stern, Ph.D., lecturer in sociology, Columbia University. A publication comprising studies of the Committee on Medicine and the Changing Order of the New York Academy of Medicine 8°, cloth, 208 pp New York The Commonwealth Fund, 1946 \$1 50

The author in this monograph furnishes an inventory, in historical perspective, of medical services now being provided directly and indirectly by government agencies on all levels—local, state and federal. The term "medical services" is understood to include all diagnostic and therapeutic, general and specialized services given to patients at home, in a doctor's office or at clinics, hospitals, schools or other institutions. It does not include community preventive measures, such as health education, sanitation, sewerage and water supply. The author has tried to indicate the pattern, scope, trends and nature of the medical services now being given and financed by all governmental agencies, and has succeeded in attaining his objective. The material is well arranged, well written and well published. This volume, as well as all others in the series, is recommended for medical, public-health and social libraries.

Allergy By Ench Urbach, M.D., chief, Allergy Department, Jewish Hospital, Philadelphia, and associate in dermatology, University of Pennsylvania School of Medicine, and Philip M. Gottlieb, M.D., associate, Allergy Department, Jewish Hospital, Philadelphia, and instructor in medicine, University of Pennsylvania School of Medicine. Second edition 4°, cloth, 968 pp, with 412 illustrations and 64 tables New York Grune and Stratton, 1946 \$12 00

The first edition of this treatise was published in 1943, and it has been found necessary to revise this second edition. Nearly 1300 new references have been inserted in the text, and the material has been increased by more than 10 per cent. Twenty-one new illustrations have been included. The following new sections have been added: Rh factor, allergic bronchitis and cough, eosinophilic erythredema and the psychosomatic aspects of allergy. Many sections have been materially enlarged. An appendix comprising a complete list of the concentrations used in patch testing has been added to the text. A double-column format has been used to cut down the bulkiness of the volume. The text is well printed with a good type on heavy coated paper. The weight of the volume could have been reduced by the use of a lighter uncoated paper. This treatise should be in all reference collections in medical libraries.

Allergy in Practice By Samuel M. Feinberg, M.D., associate professor of medicine and chief, Division of Allergy, Northwestern University Medical School. With the collaboration of Oren C. Durham, chief botanist, Abbott Laboratories, and Carl A. Dragstedt, Ph.D., M.D., professor and chairman, Department of Pharmacology, Northwestern University Medical School. Second edition 8°, cloth, 838 pp, with 34 figures and 25 tables Chicago Year Book Publishers, Incorporated, 1946 \$10 50

This standard textbook has been revised in the light of recent advances in the subject since the publication of the

first edition in 1944. The chapter on pollens and pollen allergy has been brought up to date, and pollen counts have been interpreted in the light of the newest survey methods. These new procedures in pollen counting are published for the first time. New material includes discussions on periarthritis nodosa, rheumatic fever, acute disseminated lupus erythematosus and the status of histamine and histamine antagonists in allergy. The text is well printed with a good readable type on good paper. An extensive bibliography is appended to each chapter. The volume is recommended for all medical libraries and should prove valuable to physicians interested in the subject.

NOTICES

NEW ENGLAND HEALTH INSTITUTE

The first meeting of the New England Health Institute since the war will be held at the University of New Hampshire, Durham, on June 16, 17 and 18. Train service from Boston to Durham is available about every two hours.

The program will include symposiums on public-health administration, health problems in welfare and genetics, industrial health and hygiene, vital statistics, maternal and child health, public-health nursing, communicable diseases, tuberculous control and school health and health education.

Since a large attendance is expected, all who plan to participate are urged to register early. Further information regarding the Institute will be furnished on application to the Executive Committee, New Hampshire State Health Department, Concord.

NEW ENGLAND PEDIATRIC SOCIETY

A meeting of the New England Pediatric Society will be held on Wednesday, May 28.

PROGRAM

1 15 p.m. Luncheon Vanderbilt Hall, Harvard Medical School (price, 70 cents)

3 00 p.m. Clinical Presentation of Dental Patients and Dental Subjects Paul K. Losch, D.M.D. Main Amphitheater, Children's Hospital

Members of the medical profession and students are cordially invited to attend.

5 30 p.m. Refreshments Longwood Towers

6 30 p.m. Dinner Longwood Towers (price, including tax, \$2 50) For members and friends

7 30 p.m. Child Health in Britain Dr. Alan Montreiff, Nuffield Professor of Child Health, University of London, physician, Hospital for Sick Children, Great Ormond Street, London

Members of the medical profession and students are cordially invited to attend.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MAY 29

MONDAY, JUNE 2

*12 15-1 15 p.m. Clinicopathological Conference Peter Bent Brigham Hospital

TUESDAY, JUNE 3

*12 15-1 15 p.m. Clinicoradiogenetological Conference Peter Bent Brigham Hospital

WEDNESDAY, JUNE 4

*11 00 a.m.-12 00 m. Medical Clinic Amphitheater, Children's Hospital

*12 00 m. Clinicopathological Conference (Children's Hospital) Amphitheater, Peter Bent Brigham Hospital

*2 00-3 00 p.m. Combined Clinic by the Medical Surgical and Orthopedic Services Amphitheater Children's Hospital

*Open to the medical profession

MAY 26 New England Heart Association Page 772, issue of May 15

MAY 28 New England Pediatric Society Notice above

JUNE 1-7 American Board of Obstetrics and Gynecology Page 772 issue of May 15

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The New England Journal of Medicine

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Volume 236

MAY 29, 1947

Number 22

ORAL ADMINISTRATION OF PENICILLIN*

Its Use in One Hundred and Fifty Cases

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WASHINGTON, D. C.

THE role of penicillin administered by mouth has been reported on by several investigators,¹⁻⁴ and the conclusion seems warranted that if the drug is given in sufficiently large doses, cures may be expected in susceptible infections. The optimal dose, as well as the necessity of preliminary or concurrent neutralization of the gastric acidity to avoid the inactivating influence of hydrochloric acid in the stomach when penicillin is administered orally, has been the subject of some controversy in the recent literature.⁵⁻⁷ To evaluate the latter point, penicillin blood levels were determined in a control group of over 600 subjects, plain calcium penicillin tablets containing a binding substance but without incorporated antacid, calcium penicillin tablets containing calcium carbonate, sodium citrate incorporated as buffers and plain calcium penicillin tablets with simultaneous administration of benzoic acid being used; the last combination was based on a report that benzoic acid is conjugated with glycine to produce para-aminohippuric acid and in this form competes with penicillin for excretion in the urine, thus prolonging and increasing the blood penicillin concentrations.⁸

The resulting penicillin blood levels at different intervals following the administration of these various preparations, details of which are presented more fully below, indicated that incorporation of a buffer such as calcium carbonate or sodium citrate in commercial penicillin tablets does not represent a necessary adjunct to oral penicillin therapy and that the blood levels obtained are not materially affected when these antacids are omitted. This is in keeping with the conclusion of McDermott et al.⁹ that penicillin preparations based solely on protection from acid destruction are not superior to

penicillin alone. Similarly, benzoic acid did not produce an increase or prolongation of the blood level when administered simultaneously with oral penicillin. Another point emphasized by this study was the noticeable variation in the blood levels achieved with the same oral dose of penicillin in different subjects, there also was considerable variation in the blood concentrations in the same subject from time to time when the same oral dose was employed. The penicillin titer in a given person was thus found to be somewhat unpredictable after oral administration. When the dose of oral penicillin was doubled or quadrupled, a comparable increase in the blood level did not result.

In the present series penicillin was administered orally in a total of 150 cases, including gonorrhea, subacute bacterial endocarditis, pneumonia, syphilis, cellulitis, impetigo and streptococcal pharyngotonsillitis. There were 76 children and 74 adults. Plain calcium penicillin tablets|| (without incorporated antacid) containing 25,000 units were employed in the treatment of 130 cases, and in 5 cases, tablets buffered with sodium citrate|| were used. In the other 15 cases a double gelatin capsule containing 100,000 units of penicillin was administered.

CLINICAL RESULTS

Gonorrhea

A total of 96 patients with gonorrhea were treated with penicillin by mouth. Of these, 63 were adults and 33 were children ranging in age from three to nine years (Table 1). In the adult group an arbitrary dosage schedule of 50,000 units of penicillin was administered every three hours for six doses, or a total of 300,000 units. The duration of therapy between the first and last dose was thus fifteen hours. The diagnosis was established prior to the institution of therapy by the demonstration of the organism on culture as well as on smear. Of the 63 cases treated, 57 were cured, and 5 were failures, a patient who had had negative cultures following

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||Kindly supplied by the Upjohn Company, Kalamazoo, Michigan.

therapy returned a month later with a recurrence of the urethral discharge. He had had several sexual exposures during this hiatus, and this recurrence probably represented a reinfection rather than a relapse. Among the 51 men in the group there was only one failure, whereas among the 12 women there were 4 failures, 2 of which occurred in pregnant women.

Of the 33 children all were girls except one. The total dosage employed ranged between 200,000 and 500,000 units, the majority (24 patients) receiving

carditis with penicillin administered orally when the organism was relatively sensitive. The case summary is as follows:

M P, an 11-year-old girl, was seen on April 4, 1945, when a diagnosis of interventricular septal defect and probable subacute bacterial endocarditis was made. She was admitted to the hospital on the same day.

A heart murmur had first been noted when the patient was 1½ months old. Cyanosis and dyspnea had not been present at any time. Development had been normal, and the past history was essentially irrelevant. Four weeks prior to admission she complained of easy fatigability and

TABLE 1 Results of Oral Administration of Penicillin in the Treatment of Gonorrhea

TYPE OF DISEASE	FORM OF DRUG	TOTAL DOSAGE	DURATION OF THERAPY	CURES	FAILURES	POSSIBLE REINFECTIONS
		<i>Oxford units</i>	<i>hr</i>			
Acute gonococcal urethritis	Tablet	300 000 (50,000 every 3 hours)	15	49	1	1
	Capsule	300 000 (50 000 every 3 hours)	6	1	1	—
Acute gonococcal vulvovaginitis	Capsule	300 000 (100,000 every 3 hours)	6	1	1	—
	Capsule	400 000 (100 000 every 3 hours)	9	9	—	—
	Tablet	300 000 (50 000 every 3 hours)	15	7	4	—
	Tablet	300 000 (50 000 every 4 hours)	28	10	2	—
	Tablet	200,000 (25 000 every 4 hours)	28	5	2	—
	Tablet	500 000 (50 000 every 3 hours)	36	1	—	1
Totals				83	11	2

either 300,000 or 400,000 units. There were failures in 5 cases. The gonorrheal discharge usually disappeared in eight to twenty-four hours.

In a total of 96 cases there were failures in 11—a recovery rate of 89 per cent—with the use of at least 300,000 units (50,000 units every three or four hours) in over three-fourths of the patients treated. The results are comparable to those obtained when approximately 100,000 to 150,000 units of penicillin is injected intramuscularly. The fact that 10 failures occurred in female patients is in keeping with the premise that the criteria as well as the achievement of cures of gonorrhea may be somewhat more difficult in females than in males when oral penicillin is employed. Regarding the optimal dose of oral penicillin in the treatment of gonorrhea, no categorical statement is possible until a greater number of cases have been treated.

It is important to emphasize the fact that the indiscriminate use of oral penicillin in the treatment of gonorrhea without adequate supervision should be discouraged. All patients should be serologically tested for syphilis prior to the institution of therapy, and the tests should be repeated at monthly intervals for three months to avoid the possibility of giving subcurative doses to those with associated syphilis.

Subacute Bacterial Endocarditis

It was deemed of some academic interest to attempt to treat a case of subacute bacterial endo-

carditis with penicillin administered orally when the organism was relatively sensitive. The case summary is as follows:

Physical examination revealed a well developed and well nourished girl who appeared pale but not acutely ill. No petechiae were noted. The second left upper molar tooth was decayed and loose. A harsh loud systolic murmur with maximum intensity in the 3rd and 4th interspaces about 2 cm to the left of the sternum was present and was transmitted over the entire precordium. There was an intense systolic thrill in the area where the murmur was loudest. The spleen was not palpable, and the remainder of the physical examination was negative. The temperature was 103°F, the pulse 128, and the respirations 27. An electrocardiogram was normal. A roentgenogram of the chest showed moderate enlargement of the right and left ventricles.

Three cultures taken on April 21, 22 and 24, respectively, showed the presence of thirty, forty-four and twelve colonies of *Streptococcus viridans* per cubic centimeter of blood. The strain showed a sensitivity range to penicillin of from 0.05 to 0.1 Florey units. Repeated sedimentation rates ranged between 30 and 45 mm per hour (Wintrobe), and a hemogram showed evidence of a moderate degree of anemia.

The temperature during the first 2 weeks under observation showed a daily rise between 100 and 103.4°F. Specific therapy was started on April 29. Sodium penicillin was prepared in double gelatin capsules, and 100,000 units was given every 3 hours. The patient was given a soft, fat-free diet with moderate limitation of fluids, and the feeding schedule was slightly changed so that at no time was penicillin given simultaneously with a meal. Eight hours after the initiation of oral penicillin the temperature fell from 102°F to normal and remained normal thereafter except for a transient rise to 100°F on the 9th day, at the time of the extraction of the decayed tooth.

A blood culture obtained 12 hours after the start of treatment showed no growth, and daily blood cultures taken during the entire period of 2 weeks during which the patient received penicillin were negative. Penicillinase was added to the broth in one of the cultures, and no growth was observed.

The patient received 100,000 units of penicillin as a single dose every 3 hours for 14 days—a total dose of 11,300,000

case. No toxic symptoms were observed. White-cell counts made every other day were normal, the sedimentation rate, however, remained moderately rapid. Five blood transfusions of 2.0 cc. were given over a period of 2 weeks to combat the anemia.

The patient was observed in the hospital for an additional 9 days after penicillin had been discontinued, blood cultures during that period were negative. She was discharged on May 21 and was examined every 2 weeks for the ensuing 19 months. The child was given complete freedom in her range of activity except for the avoidance of exhaustive play. The daily temperature reading was recorded. She remained afebrile, numerous blood counts were normal and blood cultures taken at frequent intervals during the follow-up period remained consistently sterile. She gained 15 pounds in weight. A roentgenogram showed no change in the cardiac dimensions.

Another patient with subacute bacterial endocarditis due to *Str. viridans* superimposed on a congenital cardiac defect was similarly treated for a month, during which 20,000,000 units was administered. Blood cultures, however, remained positive intermittently during that interval, and after what was considered a fair trial, the oral method of administration was abandoned and the intramuscular route was initiated.

In spite of the striking results obtained with the oral administration of penicillin in one of these cases, subacute bacterial endocarditis is of such gravity that the use of the oral route in this disease is not recommended. Undoubtedly, cures could be obtained in some cases, but parenteral administration offers a more reliable mode of therapy and is the treatment of choice.

Pneumonia

A series of 17 cases of pneumonia were treated with oral penicillin. Of these, 12 occurred in children varying in age from three to twelve years, whereas the remainder were in adults. A pneumococcus was isolated in 9 cases in the pediatric age group, and a hemolytic streptococcus was the causative organism in the other 3. The 5 cases in adults were due to pneumococcus, and in 2 of these positive blood cultures were obtained. Penicillin sensitivity determinations were not done. In all cases the patients were mildly to moderately ill prior to the initiation of therapy.

The usual dosage was approximately 50,000 units every three hours in 15 cases and 100,000 units every three hours in the other 2 cases. Penicillin therapy was maintained usually for forty-eight to twenty-two hours after the temperature had returned to normal. The total oral dose varied between 500,000 and 2,000,000 units in 16 cases, and in the other case 8,000,000 units was used, the average dose in the 17 cases was 1,500,000 units.

With the exception of one patient, the duration of therapy varied between one and a half and seven days, with an average of four and a half days per patient. The temperature returned to normal by crisis usually within twelve to thirty-six hours after the initiation of therapy in 14 cases, and prompt clinical improvement was observed. In no

case was a recurrence of fever or leukocytosis, or both, following termination of therapy noted. There was no perceptible difference between the response of the adults and that of the children in this series.

In 3 cases the temperature came down by lysis during a period ranging from three to eight days, and slow resolution of the pneumonic process was observed, requiring six to twelve days. In 1 patient, an acutely ill eleven-year-old boy, pneumonia due to a Type 14 pneumococcus was complicated by an empyema at the time of admission. He received 480,000 units of penicillin orally each day, a total of 8,000,000 units being given for the eighteen-day interval during which therapy was maintained. In addition, 40,000 units of penicillin was injected into the pleural cavity on three alternate days. Recovery was gradual, the temperature slowly returning to normal by lysis over the course of eight days and the empyema subsiding.

The results obtained with penicillin administered orally in the treatment of pneumonia both in adults and in children indicate that, in the majority of cases, such therapy is efficacious if the drug given is in sufficiently large doses. The total dose used was approximately three to four times the parenteral dosage usually employed. The recommended dose must be predicated on the severity of the pneumonia at the time of admission, a schedule of 50,000 to 75,000 units every three hours for a total of 1,500,000 to 2,000,000 units, however, seemed to be adequate in the majority of cases, although it should be pointed out that two thirds of the patients were children. Pneumonia complicated by empyema is probably best treated by parenteral rather than oral administration of penicillin, together with intrapleural instillation of the drug.

Syphilis

Penicillin was administered orally in 3 adult cases of early syphilis. The dosage schedule consisted of 50,000 units of calcium penicillin in tablet form every four hours for twelve days, or a total of 3,600,000 units.

In 1 case the quantitative Kahn titer was 20 units prior to the initiation of therapy, and the serologic tests became negative within three months, a relapse occurred two and a half months later, however, and the serologic test was still positive after a seven months' follow-up period.

In the other cases, the quantitative serologic estimations were 120 and 260 Kahn units respectively prior to treatment, and in both cases the tests were negative after a six to eight months' follow-up period. One of these patients experienced a mild Herxheimer reaction.

In 10 other patients with syphilis, the lesions that had been dark-field positive became dark-field negative within eighteen hours after the administration of 100,000 units of penicillin by mouth. Herx-

heimer reactions were noted in 3 cases. No attempt was made to treat the patients fully with penicillin by mouth, since the object of this preliminary trial was to determine the rapidity and the dose required to produce dark-field negativity.

In the 3 cases fully treated penicillin given orally produced serologic reversals with a total dose of 3,600,000 units. In 1 case, however, a relapse occurred within five and a half months, and the follow-up examination in the other 2 cases was too short to permit any statement regarding the permanency of the negative serologic tests obtained. It is possible that a total dose of 5,000,000 to 10,000,000 units is required in early syphilis if penicillin is administered orally.

In view of the several complexities in the management of a case of syphilis with penicillin and the relatively high percentage of relapses, the demonstration of serologic reversals with the oral administration of penicillin is probably of academic interest only, at least for the present, except in cases in which the patient is treated in a hospital and observed closely, with serial quantitative serologic examinations following termination of therapy. Unless it is rigidly controlled, such therapy introduces the additional hazard of attempts at self-medication and the administration of subcurative doses.

Miscellaneous Infections

Twenty-three cases of cellulitis in children ranging in age from three to eight years were treated with oral penicillin. The cellulitis involved various sites, some cases having associated abscess formation. A three-hour divided dosage schedule ranging from 25,000 to 50,000 units was employed, with the total dose varying from 240,000 to 1,110,000 units. Hot moist compresses were used concomitantly, and when fluctuation occurred, the area was incised and drained. The organism in the majority of cases in which pus was obtained was either hemolytic staphylococcus or streptococcus. The results paralleled those obtained with parenteral administration of penicillin when the drug was given in approximately one third to one fourth the oral dose.

Five cases of impetigo in infants ranging from two months to two years of age showed a prompt response within two to four days after the oral administration of penicillin varying in dosage from 400,000 to 900,000 units.

Four cases of acute pharyngotonsillitis due to a hemolytic streptococcus responded well to 800,000 units of penicillin administered orally on a dosage schedule of 50,000 units every three hours.

SUMMARY

Penicillin was administered orally in a total of 150 cases, including gonorrhea, subacute bacterial endocarditis, pneumonia, syphilis, cellulitis, impetigo and acute pharyngotonsillitis.

The commercial penicillin tablets used in this study were effective in penicillin-susceptible infections if given in sufficiently large doses.

The fundamental principles of penicillin therapy when the oral route is employed do not differ materially from those attendant on the parenteral administration except for the greater oral dose required.

In view of the relatively small number of cases as well as the age range, in this series, no categorical statement is possible regarding the optimal oral dose of penicillin. The dosage varies from case to case, depending on the severity and type of infection. The inadvisability of indiscriminate oral administration is emphasized.

REFERENCES

1. Burke F G, Ross S., and Strauss C. Oral administration of penicillin preliminary report. *J A M A* 128 83 86 1945
2. Ross, S. Burke F G and McLendon, P A. Penicillin by mouth report of clinical trial. *J A M A* 129 327 332, 1945
3. Finland M, Meade M., and Ory, E M. Oral penicillin. *J A M A* 129 315-320 1945
4. Cutting, W C, Halpern R. M., Sultan E H, Armstrong C D., and Collins C L. Administration of penicillin by mouth with results in treatment of gonorrhea. *J A M A* 129 425-432 1945
5. Bunn P A, McDermott, W, Hadley, S J., and Carter A C. Treatment of pneumococcal pneumonia with orally administered penicillin. *J A M A* 129 320 327, 1945
6. Gyorgy P, Vandegriff H N, Elias, W, Colho, L G, Barry, F M., and Pilcher, J D. Administration of penicillin by mouth preliminary report. *J A M A* 127 639-642 1945
7. Seeberg V P., and Collen M F. Calcium carbonate as antacid for oral penicillin. *Science* 102 225 227, 1945
8. Bronfenbrenner J and Favour, C B. Increasing and prolonging blood penicillin concentrations following intramuscular administration. *Science* 101 673 1945
9. McDermott, W, Bunn P A, Benoit, M., Dubois R. and Reynolds M E. Absorption of orally administered penicillin. *Science* 103 359 361 1946

THE TREATMENT OF HYSTERIC AMNESIA BY PURELY PHARMACOLOGIC MEANS

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PERHAPS no condition is fundamentally so psychologic and without any obvious organic background as hysteric, or functional, amnesia. This condition usually arises abruptly and may disappear as suddenly. It is difficult to conceive of an organic or physiologic basis for a memory loss in which the whole or a large part of the past, often including personal identity, so far as the consciousness of the patient is concerned, is lost for long periods and without the slightest evidence of any neurologic disturbance.

Several kinds of treatment have been instituted for this condition. One is, simply, by the stimulation of the association processes and by psychologic mechanics, to reopen the shut-off field of memory. The second and popular means utilizes hypnosis, the effort being made to delve into the unconscious, to reach motivations for the "escape" process and, by suggestion during and after hypnosis, to cure the amnesia. Still another method is that of psychoanalysis, which in general follows the main directions of this elaborate process, seeking to release the tensions and obstructing mechanisms and thus to integrate the split personality. More recently pharmacologic methods have been developed that have been used mainly in military service and date back earlier than Lindemann's¹ initiatory work on amylal sodium. By the production of narcosis and either by analysis²⁻⁴ or synthesis⁵⁻⁷—these terms indicate the attitude of the worker rather than any really new development—the technic seeks to reintegrate the patient. The workers with these methods have stressed the psychologic factors, since the emphasis has been laid on the assumed fact that the narcosis, or drug effect, merely gives a handle by which psychotherapy can be applied.

In the treatment of 3 recent cases of hysteric amnesia in private practice, an effort was made to exclude psychologic methods and narcosis and to use drugs that have profound central effects. In certain researches on the effect of amphetamine (Benzedrine) sulfate and similar drugs on amylal sodium narcosis, it was noted that when the two drugs were given simultaneously, narcosis was not reached, a mood was produced that can be called exhilaration, or something akin to it, and perhaps more pertinently, a garrulity was noted, often of great intensity in a good many of the patients. Therefore, I utilized the combined effect of amphetamine sulfate—or of Pervitin Hydrochloride

(d-N-methyl amphetamine hydrochloride), which is a similar drug and which on the basis of the literature and personal experience appears to have a greater central effect than amphetamine, as well as producing a greater tendency toward loquacity—and amylal sodium given by mouth in such combined dosage that nothing that could be called narcosis resulted, since only 1 patient became even sleepy. The reorganization of the memory, which was spontaneous and immediate in 2 cases, was brought about in 1 case by simple questions such as those indicated in the case reports presented below. In all cases an effort was made to exclude any analysis of the psychologic situation of the patient both prior to and after the amnesia. Only enough history was taken to establish a diagnosis, and treatment was instituted immediately. No explanation was made, and the therapist excluded his personal influence so far as possible. The results clearly show that pharmacologic methods alone are sufficient to restore the memory of a patient suffering from a profound hysteric or functional amnesia, and that the successful treatment, so far as the immediate problem of restoring the lost memory is concerned, is of the simplest possible order. The treatment of these cases demonstrates a fact that does not seem to require emphasis—namely, that psychologic states are as clearly accessible to pharmacologic treatment as to any other form of treatment.

Two of the cases were post-traumatic, Case 1 arose without any such etiology. In all cases, speculation might easily reveal deep and dynamic psychologic causes.

CASE 1 A 45-year-old Jewish man found the nature of his work in a defense plant intolerable or, at any rate, disagreeable. He complained a good deal and said that there was much anti-Semitism and that other workers played tricks on him. He grew increasingly irritable, developed insomnia and other neurotic symptoms, and one day became quite violent, excited and noisy while at work. He was taken to a hospital for a short time, after which his family took him home. He had a complete amnesia, which stubbornly persisted after his excitement had entirely disappeared. The amnesia was not only for the period of his work at the defense plant, but for practically everything in the previous 10 years. He could remember his childhood. He did not remember his marriage, nor did he acknowledge his wife stating that he did not know her. This attitude was maintained unswervingly for about a month, when I saw him for the first time.

The patient was in excellent physical condition, presenting no signs of organic brain disease—in fact, it is clear that such an amnesia is not possible as a direct result of an organic brain accident or injury. From the time of the onset of his illness to the time when I first saw him, his recent memory was intact—that is, the recent experiences were perfectly well assembled, organized and recalled, although

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past memories and associations for at least 10 years were entirely absent from his consciousness.

Without in any way indicating the purpose of the treatment, I placed the patient and his wife in a separate room in my office suite. He was then given 0.2 gm (3 gr) of amytal sodium and 15 mg of amphetamine sulfate by mouth. I left the room and returned in 45 minutes. I then asked the patient if he recognized the woman to whom he was talking. He immediately answered with a long and detailed statement, speaking rapidly and with some degree of incoherence, that certainly he recognized her. She was his wife, he went on to answer questions about his past life, sometimes with a slight hesitation, and at other times with none whatsoever. He talked about 1 hour, almost constantly, and at the end of the time had practically reassembled his whole past.

This patient was last seen in June, 1942, and has remained well since then, there has been no gap whatever in his memory.

CASE 2 In this case, the amnesia was much more complete, since the patient completely forgot everything in the past history, including his own identity. This patient, a 50-year-old foreman in a factory, was a skilled mechanic whose past history was entirely free from any overt psychopathology. He was regarded as a well organized, industrious, self-disciplined and controlled person who had nothing resembling a neurosis of any kind. About a year before the time he was first seen, one of his sons had given him a great deal of trouble, which hurt his decided pride in his family name. Although he seemed concerned and humiliated, he continued to work steadily and satisfactorily, carrying out his responsibilities as well as ever. Then while at work he received a blow on the head that was not severe enough to create unconsciousness but was of sufficient momentum to daze him. The back was wrenched at the same time. He complained of severe headache but returned to work the next day, seemed forgetful and confused and complained of the pain in the back and the head almost constantly.

Within 48 hours he became "very wild," ran out of his place of work, assaulted a policeman and talked wildly about the people who were trying to destroy him and his family. He was overpowered, given sedation and quieted down quickly. He was taken home and from that time on until he came to see me 6 weeks later, he presented a complete amnesia. He remembered nothing of his past. He accepted his name as being his own, but he did not remember it. He did not recognize his wife, two devoted sisters or his children. He knew nothing whatever of the place in which he had worked, nor was he able to give any information about his past, his education, his training, his work or any of his experiences. When he came to the office, he stated, "This woman says she is my wife, and this woman states that she is my sister." He was not in any way friendly toward them. He was not affectionate, in fact, he rather resented their solicitude. His answer to every question concerning his past was "I don't remember. I am told I am so and so, but from my own knowledge I do not know who I am." It was stated, and he agreed, that some things in the town in which he lived seemed familiar to him, and he had on one occasion used the name "Bill" to denote a man whose name was Bill, but he could not give any information concerning this man. He said that this memory had "popped" into his head. It was clear that this amnesia was functional and that no organic lesion could wipe out a man's entire past and leave him entirely coherent and relevant in his speech and without any defect in his recent memories.

The procedure followed in Case 1 was repeated, except that instead of amphetamine sulfate, 10 mg of Pervitin was used, in combination with 0.2 gm of amytal sodium by mouth. The patient was left in the room with a sister and his wife, and I passed on to the care of other patients, until 45 minutes had elapsed. When I returned, the patient, after a short period of slight drowsiness, was talking freely to his wife and sister and recalling spontaneously, to their delight, his past experiences. He passed from one theme to another with great rapidity, remembering things that they had forgotten. He was entirely at ease with them and not only knew them but felt that they were his kinfolk. When I addressed him, he asked them who I was and how he happened to be in the examining room. Within a minute or two, however, he had recalled the circumstances of his coming to a doctor's office, and all the gaps of his memory were soon in a fair way to be filled in. When he reported the next

day, the amnesia had entirely disappeared, and so far as his family could determine, he was entirely normal. He talked of his son's delinquency with some sorrow, but with no undue emotion. No attempt was made to explain the situation to him, largely because I am of the opinion that no adequate explanation can be given, and moreover, because in these cases the attempt was made to cure hysterical amnesia with no psychotherapy.

This man was last seen in May, 1944, and has remained entirely well since then. If there is anything psychopathologic left to be cured by any other means, neither the patient nor his family are aware of it.

CASE 3 A 14-year-old girl, in her 1st year of high school, was recently seen. She had had no emotional difficulties any kind so far as was then known. The family, although poor, lived in harmonious and adequate circumstances. The parents were as kind and understanding as most parents. Her school work was average in its marks and presented no apparent special difficulties. She had plenty of friends. She partook of social affairs freely and joyously. She was too young to have any steady boy friend, but she liked boys and was attractive to them.

Three weeks before I saw her, she went to school in the usual way. It was the morning of a great snow storm. She did not reach the school, and the day went by without an word from her. The parents became alarmed and called the police, and the patient was finally picked up wandering in a distant part of the city. She did not know her name and had no memory of her past. She did not recognize her parents although she accepted the statement that they were her mother and father. She could give no account of what had happened to her. She recognized the fact that other children in the household were her brothers and sisters and the people who came in were her friends, but the sense of familiarity—that is, a chain of memories with a feeling of familiarity—was absent. She seemed apathetic and dull, did not show her usual animation, and was naively bewildered. She remained, practically speaking, in this condition until she was brought to see me. A careful physical examination revealed no evidence of any organic disorder, and again it must be stated that it is not probable that any organic disorder could have produced such a complete amnesia with unimpaired consciousness for the present and its events.

The same procedure was followed as in Cases 1 and 2, except that on the first occasion 0.2 gm of amytal sodium and 10 mg of amphetamine sulfate were used with relatively little effect, the patient could recall the school she had attended recently, but questions had to be asked for every fact obtained—for example, when asked whether she remembered her teacher's name, after a long pause she assented and gave the name. There was little spontaneous recall, and although some progress was made by the question-and-answer method, the results were not satisfactory.

The patient reported the next day, when 0.2 gm of amytal sodium and 10 mg of Pervitin were administered. In about an hour she was questioned about her past. She answered quickly, easily and interestedly. Spontaneously she went on from one fact to another and gave details about the people she had known, often with a humorous twist. She proceeded from the subject brought up to a related subject, bridging the gap with a statement such as "Oh, yes, and now I remember." By the end of this interview she was gay and, moreover, expressed her gratitude to the physician for his help. She recognized that she had lost her memory and went on suddenly to tell how the amnesia had happened—in other words, to fill in the events of the day on which her memories had become displaced. On her way to school that morning, as she reached a place near it, several boys had thrown snowballs at her. In her frightened attempt to dodge the missiles, she had slipped and fallen heavily on the ice, striking her head. She had got up dazed and from that time had wandered around in the amnesic state. After her recovery, however, she was able to give details of the places that she had visited, and as she related the happenings of the morning, her face became quite animated and excited while she went from event to event.

This child required one more treatment before all the gaps in memory were filled in, and she completely re-integrated her past and present life and re-formed the bonds of recognition and easy familiarity with the people and things of her milieu. She then came in to see me with a statement

of the conditions of her school attendance, which gave at last a plausible explanation of her break up into hysteric amnesia on the occasion of the snow-ball throwing. There were four "tough" girls in her class who took a delight in malicious teasing and assaulting her. They mocked and defied her genteel manner. They tripped her as she went by them, and on one or two occasions, they roughly handled her, so that going to school each morning was an ordeal and there took place a greater and greater reluctance to enter the school portals. She reached school each day in a state of acute terror, and this terror persisted throughout the whole person. Thus, the main conscious feature of her school attendance was the fear of what these girls might do next. It is conceivable that on the basis of this fear, the assault by the boys with snowballs and her consequent fall brought about the dissociation of hysteria. The fall was merely the immediate physical and psychic trauma to a personality already disorganized by chronic anxiety. This is true of the other cases and probably also of the amnesias that take place in war.

This patient was last seen in March, 1945, and has recovered well since then.

It is not contended that all cases of hysteric amnesia are treatable by this simple means. Certain ones are far more complicated in psychologic mechanisms and social entanglements than the cases cited above. For example, a young woman whose mother was psychotic and had received shock treatment and whose husband had been discharged from the Army with a diagnosis of psychoneurosis lived in a domestic atmosphere of turmoil and unhappiness that might have been expected from the fact that she and her husband lived with the mother. There were constant bickering, quarreling and extreme emotional tension in the household. From time to time she had unconscious attacks, which were really hysteric attacks and following which there was an amnesia for a considerable period of the time prior to the attack. Each attack was easily cleared up by the use of these drugs, but the treatment in no way prevented further attacks from taking place. During the amnesia, there was stuttering, which was also helped by the drugs but which tended to recur during another attack of amnesia. In this case treatment had to be much more drastic than the simple administration of the drugs, with a change in the whole setup between the patient and her husband and her mother before any lasting therapeutic result was obtained. It should be added that a good deal of so-called "hysteric amnesia" is malingered, and one must be on one's guard at all times in judging whether or not an amnesia is hysteric or faked.

The essential feature of the treatment of the cases presented above seems to have been in the breaking down of abnormal inhibition and personality attitude that takes place under the influence of powerful drugs and, perhaps more importantly, the drive given by these drugs to communication, the uncon-

scious reticence that is probably the basis of the amnesia being dissolved. To speculate quite without proof, something is set up that says, in essence, "I do not want to remember, I cannot remember." The impetus of the drugs removes this negativism and thus brings about cure. In catatonic dementia praecox, as shown first by Lindemann¹ with amytal sodium narcosis, the same result is obtained temporarily, in that the patient who has been noncommunicative talks freely after the drug narcosis, but, as the effect of the drug wears off, the catatonia reasserts itself. Since hysteric amnesia is a relatively mild disorder, the effect of the drugs seems to be lasting.

The pharmacologic effect of the two drugs used, as pointed out in previous publications,^{8,9} is reciprocal. As Lindemann's work showed, amytal sodium breaks down negativism and the mutism that goes with it, whereas amphetamine sulfate and, especially, Pervitin not only prevent the narcosis but also have a definite pushing effect, synergistically with the sodium amytal, on the verbal association processes. The combination seems to be ideal wherever one desires to increase communication and especially in the great field of the psychologically hidden.

SUMMARY

Three cases of undoubted hysteric amnesia occurring rather suddenly in relatively normal people are presented. The effort was made to exclude psychotherapy and also the use of narcosis. To accomplish these ends, a combination of amphetamine (Benzedrine) sulfate or an equivalent drug and amytal sodium was administered in such doses as not to produce narcosis. Increased communication took place, and there was immediate or relatively immediate dispersal of the amnesia.

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REFERENCES

1. Lindemann E. Psychopathological effect of sodium amytal. *Proc Soc Exper Biol & Med* 28:864-866, 1931. Psychological changes in normal and abnormal individuals under influence of sodium amytal. *Am J Psychiat* 11:1033-1091, 1932.
2. Horsley J. S. Narco-analysis. *Lancet* 1:55, 1936.
3. *Idem*. Pentothal sodium in mental hospital practice. *Brit M J* 1:938, 1936.
4. Wilde J. F. Narco-analysis in treatment of war neuroses. *Brit M J* 2:3-7, 1942.
5. Grinker R. R., and Spiegel, J. P. Narco-synthesis: psychotherapeutic method for acute war neuroses. *Air Surgeon's Bull.* 1:1-5, 1944.
6. *Idem*. Brief psychotherapy in war neuroses. *Psychosom & Med* 6:125-131, 1944.
7. Grinker R. R. Treatment of war neuroses. *J A M A* 126:142-145, 1944.
8. Myerson A., Loman, J., Runkel, M., and Lisses M. F. Effect of amphetamine (benzedrine) sulfate and pargidine hydrobromide on sodium amytal narcosis. *Ann Eng J Med* 221:1015-1019, 1939.
9. Myerson A. Reciprocal pharmacologic effects of amphetamine (benzedrine) sulfate and barbiturates. *Ann Eng J Med* 221:561-564, 1939.

METASTATIC MELANOCARCINOMA INVOLVING THE SMALL INTESTINE AND BRAIN*

Report of a Case, with a Discussion of Malignant Tumors of the Small Intestine

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REVIEWING the recent literature concerning diseases of the small bowel, one is impressed with the infrequency of reports of malignant tumors. Narrowing the field of interest to melanomas occurring in the small bowel certainly increases the task of locating appropriate material in many cases. With these points in view this paper is directed toward a broad comparative survey of the occurrence of malignant lesions in the small intestine, with special emphasis on melanomas.

In about 10 per cent of cases at autopsy a carcinoma is found somewhere in the body. A review of 137,174 cases gathered from various hospitals by Shallow, Eger and Carty¹ revealed primary malignant tumors of the large intestine in 3.66 per cent, the small intestines being named the origin of malignant growths in only 0.098 per cent. Both carcinoma and sarcoma may develop in the small intestine. Shallow et al.¹ also state that 3 per cent of intestinal carcinomas and 60 per cent of intestinal sarcomas occur in the small bowel. Carcinoma is twice as frequent as sarcoma in this location, despite the percentages cited above, since sarcoma of the intestines is such a rare finding. The importance of this distribution and its effect on the signs and symptoms produced and on the success of diagnosis are referred to below.

Adenocarcinomas compose about 90 per cent of the small-bowel carcinomas and in most cases are of the napkin-ring type, but they may be polypoid and ulcerative.² To step into more controversial territory it may be mentioned that many authors have reported cases of malignant carcinoids in the small intestine and have attested their malignancy by giving evidence of widespread metastases.³⁻⁵ Most authors agree that there is a rather pronounced tendency for the carcinoid to be malignant when it is located in the gastrointestinal tract in sites other than the appendix, although the appendiceal lesion behaves like any benign tumor.

A melanoma in the small intestine is a rare tumor, whether it is regarded as primary in the bowel or as a metastasis from some other site. Herbut and Manges⁷ in a survey of the literature cited only 25 cases, of which 9 were reported as primary in the small intestine and 16 as metastatic lesions. Ewing⁸ states that melanoma of the intestine occurs

almost exclusively in the rectum. The rarity of the lesion can easily be shown by the fact that the general texts of pathology make no mention of such a lesion of the small bowel.

It is interesting to note that several authors have made attempts to explain the relative infrequency of small-bowel as compared with large-bowel tumors. Fraser⁹ suggests that the alkalinity of the intestines, the fluidity of the contents, the lack of sharp bends and the absence of prolonged stasis may explain in part the low incidence of neoplasms in the small bowel. Rankin and Mayo¹⁰ presented the hypothesis that the tumors arise from embryonal rests or develop as a result of some pathologic changes in Brunner's glands. As in all other conditions in which the etiologic agents are still obscure the possibility that some hormonal influence is present must be considered. Perhaps the contents of the bile, the pancreatic juice or the succus entericus plays some part in protecting the small bowel by furnishing an environment adverse to tumor growth.

There is considerable disagreement among the various writers about which areas of the small intestine are involved most frequently. According to Swan,^{11, 12} carcinoma involves the duodenum and ileum with equal frequency and attacks the jejunum less often. Shallow's¹ survey of a large number of cases is somewhat at variance with this statement—he has found that the malignant process involves the three parts of the small intestine with equal incidence and that the ileum ranks lowest for carcinomas but highest for sarcomas. Within the duodenum, carcinoma is most frequent in the second part, less frequent in the first part and quite rare in the third part.¹³ The carcinomas found in the first part of the duodenum are usually lesions that have developed as a result of the extension of carcinoma of the head of the pancreas or, more rarely, carcinoma of the pyloric end of the stomach into the duodenum via the subserosal lymphatic vessels or by implantation of the serosa.¹⁴ The high incidence of tumors occurring in the second segment is explained in part by the entrance of the common bile duct into the duodenum. It is a known fact that the junction of two different types of epithelium predisposes to the development of cancer,¹⁵ as attested by the frequency of carcinoma of the lip or rectum developing at the mucocutaneous junction. It is usually stated that the sarcomas are oftenest found in the terminal ileum and jejunum. One cannot make a definite statement regarding the

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frequency of melanomas in the various areas of the small intestine, since the vast majority of the melanomas have been reported as secondary lesions metastatic from some other focus. Thus, chance alone determines whether the tumor emboli lodge in the blood and lymphatic vessels supplying the duodenum, the jejunum or the ileum. Few authors have been so bold as to claim discovery of a melanotic tumor primary in the small intestine.

The order of metastasis of primary intestinal cancers to other organs seems to be as follows: the mesenteric lymph nodes and peritoneum, the liver, the lungs, the long bones, the dura mater and the spinal cord.¹⁸

The patients who suffer from carcinoma of the small bowel are usually within the classic cancer-age group. Figures by Fraser⁹ give the average age as between fifty-two and fifty-six years. Ullman and Abeshouse claim that thirty-three years is the average age for sarcoma of the small bowel. Men and women seem to be affected by the malignant tumors with equal frequency, although the lesions seem to develop at an earlier age in women than in men.

CASE REPORT

M. C., a 55-year-old woman, was admitted to the hospital on February 14, 1946, because of faintness, nausea and vomiting on two occasions during the previous 2 months. In December, 1945, the patient had fainted after smelling cigarette smoke. She was unconscious for a few minutes and on awakening vomited three times. She was taken to a hospital, where she remained only a few hours. About a week prior to this episode, the patient had also fainted after smelling cigarette smoke, had been nauseated and had vomited. She felt weak and dizzy. She had had no convulsions at any time but had noticed incontinence. She suffered from frequent dizziness accompanied by dimness of vision and also had generalized severe headaches. She had a poor appetite and could take only liquids.

Neurologic examination revealed the cranial nerves to be intact. All tendon reflexes were hypoactive, and the Babinski reflex was negative. The abdominal reflexes were not elicited. There was difficulty in distinguishing between sharp and dull sensations in both lower extremities. The patient could not distinguish the position of toes. Romberg's sign was positive, indicating impaired strength in the left lower extremity. The pupils reacted to light and accommodation. There was no strabismus. All other findings were essentially negative, except that the patient had no regular bowel movements and had to take laxatives at least once a week. She stated that five years previously a carcinoma of the shin bone of the left leg had been surgically removed. In the hospital a neuro-ophthalmogram was done. The patient did not rally afterward and gradually failed; she died on February 21.

Autopsy. Post-mortem examination showed the body of a well-developed, well-nourished woman who appeared to be of stated age. There was a well-healed, 5-cm-long scar on the medial aspect of the left leg. On section there was no free fluid in the abdominal cavity. The liver edge extended two fingerbreadths below the right costal margin. There was no free fluid nor evidence of adhesions in either pleural cavity. Examination of the heart disclosed no gross pathological findings throughout the chambers, valves and appendages. Both coronary ostia were patent. The aorta showed a moderate amount of atheromatosis. The left lung was slate blue, with the usual anthracotic pattern. The cut surfaces were feathery and dry. The right lung showed a similar picture. The hilar lymph nodes were normal in size and consistence. The liver was smooth and reddish brown. It was of normal consistence, and section disclosed mild congestion. The gall bladder revealed nothing of importance.

The spleen was grayish blue, and on section the pulp was fleshy and congested. Section of the pancreas and adrenal glands showed their respective normal architecture. The kidneys, which were slightly smaller than usual, were purplish red. The capsule stripped with little difficulty and revealed a beginning fine cortical granularity. On section the corticomedullary ratio was preserved. The ovaries were small, grayish white and dense. The left ovary presented a cyst measuring 1.5 cm in diameter. The uterus was somewhat atrophic. The esophagus and stomach showed no gross abnormalities. In the first part of the ileum, three ulcers across



FIGURE 1 Photograph of the 'Ulcers' in the Ileum

the circumference of the bowel were visible. Each ulcer was separated from the other by about 5 cm of normal mucosa. The lesions showed raised, rounded edges and were shallow (Fig. 1). The floors of the ulcers were covered with a slight greenish-gray exudate. Each ulcer measured about 2.5 cm in diameter. The surrounding mucosa was not infiltrated. The indurated edge of each ulcer was well delimited. One centimeter distal to the last large ulcer, a smaller ulceration, 0.5 cm in diameter and similar to the others in all respects but size, was noted. On the serosal surface over each ulcer there were a few yellowish nodules of pinhead to split-pea size that appeared to correspond with the edges of the ulcerations. There was no penetration or thickening of the serosa over the craters of the ulcers. Otherwise, the remaining small bowel and large intestine were not remarkable. The lymph nodes showed no involvement on gross examination. The lesions were grossly diagnosed as multiple ulcers of the first part of the ileum of undetermined etiology.

The histopathological diagnoses were bronchial dilatation, emphysema, atelectasis and bronchitis of the lungs, central congestion and beginning fatty metamorphosis of the liver, congestion, reticulum fibrosis and capillary sclerosis of the spleen, congestion of the adrenal glands, periductal fibrosis and slight lipomatosis of the pancreas, congestion of the kidneys, with beginning arteriosclerosis, follicular cyst left ovary, and partially necrotic tumor tissue of the ileum. The tumors presented a somewhat alveolar pattern (Fig. 2). In some areas the arrangement could be called pseudopapillary. The cells were large and polyhedral. A few small anaplastic cells were seen. The nuclei were hyperchromatic, and a moderate number of mitoses were apparent. A small amount of brownish-yellow pigment was seen in some fields, being contained within a somewhat more fusiform type of cell. The tumors contained a few small non-invaded blood vessels. The lymph spaces in the serosa of the intestine showed clumps of tumor cells. The diagnosis was melanocarcinoma.

Sections through the midbrain and cerebellum revealed hemorrhagic areas in the raphe of the peduncles and in the superior portion of the right cerebellar hemisphere. Section through the corona radiata showed a spongy lesion (3 by

4 cm) with somewhat ragged but well defined borders (Fig 3). The lesion was dark brown. Similar lesions were observed in the left frontal operculum and in the right temporo-occipital region, and others were encountered in the right temporal lobe at the level of the anterior commissure, in the occipital lobes and in both frontal lobes. The histologic picture of the tumor masses was identical with that of the tumors found in the small bowel, but a more pseudo-peritheliomatous pattern was present*.

In this case there were no abdominal symptoms or signs that could be attributed directly to the intestinal lesions. There was a history of a "carci-

noma" removed at an earlier date. Four ulcers in the ileum were diagnosed microscopically as melanocarcinomas. There were multiple melanocarcinomas involving the brain. It is unfortunate that complete information concerning the tumor removed at an earlier date could not be obtained, since classification of the tumor would probably have aided in the solution of some of the problems presented.



FIGURE 2 Photomicrograph of a Section of One of the Tumors of the Ileum ($\times 80$)

noma" removed at an earlier date. Four ulcers in the ileum were diagnosed microscopically as melanocarcinomas. There were multiple melanocarcinomas involving the brain. It is unfortunate that complete information concerning the tumor removed at an earlier date could not be obtained, since classification of the tumor would probably have aided in the solution of some of the problems presented.

DISCUSSION

A primary consideration in melanoma is its relation to the pigmented nevus. Benign pigmented nevi, or pigmented moles, are seen on the skin of almost every man, woman and child. The average person is born with approximately fifteen to twenty of these spots.¹⁷ They may be light or dark, flat or raised and hairy or smooth, and they may vary

*We are indebted to Dr. Walter Freeman for the information concerning the brain lesions.



FIGURE 3 Photograph of the Brain, Showing the Various Tumors

from a fraction of a millimeter to several centimeters or more in size. They are quite innocent and demonstrate no invasive qualities. They occur particularly on the face, neck and back but are frequently seen in large numbers on the extremities. These benign nevi are usually responsible for no more discomfort than any other slight skin blemish. In some cases, however, innocent nevi undergo malignant changes, generally owing to the constant irritation of repeated rubbing or cutting. Therefore, the nevi that are likeliest to become malignant are in areas of the body exposed to continual chafing and disturbance—for example, on the neck at the collar line, on the heel of the foot or on the face in the path of the razor's edge. A nevus that has undergone malignant change is known as a malignant melanoma or simply a melanoma, a term first used in 1836 by Carswell. Approximately 32 per cent of the melanomas arise from nevi.¹⁸ Studies on the early changes of nevi into melanomas show that the important signs and symptoms of a potential malignant process consist of a history of trauma, itching, growth of the nevus, pain and inflammation.¹⁹ The melanomas of the skin usually do not develop into large tumors despite their high malignancy.

A characteristic trend seems to be the tendency toward a rather long latent period between the operative removal of the melanoma of the skin and any evidence of visceral metastases. According to DeCholnoky¹⁵ metastatic lesions occur within six months to two years of the recognition of the skin lesion. Many exceptions occur, however, and metastasis from a melanoma of the skin has been reported as late as ten to twenty years after removal of the primary tumor. This latent period is shown clearly by the case presented above, in which signs of metastasis were delayed for five years.

Metastasis usually begins by an infiltration into the surrounding skin area, and the first metastatic lesions are usually in the skin. Next, the regional lymph nodes are involved. The tumor cells multiply within the lymph nodes, replacing the normal architecture, and eventually invade the capillaries within the node. Further extension then occurs rapidly via the blood stream.¹⁸ Although this is the usual method of spread, an early, direct blood-stream invasion may occur. Ewing⁸ thought that the method of early spread is usually by the lymphatic vessels. He further claimed that hematogenous spread is late and generally extensive, missing hardly an organ. It is interesting to note that in the case presented above only two organs were involved, if the lesions in the ileum and brain are regarded as metastatic. Obviously, any form of lymphatic spread can be excluded, since there were no obvious lymphatic connections between the areas of tumor involvement. The only possible method of metastasis in this case seems to have been that of hematogenous dissemination. Contrary to Ewing's statement that a large number of organs are affected when tumor spread is via the blood, however, only two organs were involved. No logical explanation can be advanced to explain this discrepancy. No definite sequence of spread to the various organs can be given in cases of hematogenous spread, since the lodging of tumor emboli in the various organs is largely a matter of chance.

Another common site for the development of melanomas is the eye. Ewing states that about a third of all the melanomas have their origin in the choroid layer of the eye. Metastasis may be delayed in this type, just as in the melanoma of the skin. Melanomas also arise from the brain, the adrenal glands and the rectum at the mucocutaneous junction.

Few reports have proposed the presence of primary melanomas in the small bowel. Herbut and Manges,⁷ in a review of the literature on intestinal melanomas, located only 9 such cases. Obviously, the plausibility of such reports depends on a concept of the tissue of origin of the melanoma that is by no means definitely established. There are two chief schools of thought, one group stressing the role of the melanoblast as the chief cell involved in the formation of the tumors and the other,

headed by Masson, championing the cells of the Meissner and Merkel-Ranvier complexes that occur in the skin. Laidlaw²⁰ has made an extensive study of melanoblasts and the dopa reaction on material at autopsy and has concluded that melanoblasts, which he considers responsible for the tumor formation, do not exist in the small intestine. Furthermore, there are no melanoblasts in the colon or in the rectum above the mucocutaneous junction. Therefore, he concludes that the occurrence of primary melanomas above this junction is improbable and that if these tumors do occur they must arise from misplaced islets of ectoderm. We are not aware of any reports that the Meissner and Merkel-Ranvier complexes exist in the intestinal walls, and on this basis, a neurogenic origin of a melanoma in the small intestine can be ruled out. Thus, it appears to be quite risky to diagnose a primary melanoma of the small bowel on the basis of present knowledge. Herbut and Manges⁷ point out that the eyes, which, as previously mentioned, are often the source of melanomas, are usually not examined adequately enough in the routine autopsy to rule out melanoma of the eye. Consequently, they conclude that "without a thorough examination of the eyes a diagnosis of primary melanoma of the small intestine should not be made." It is our belief that on the basis of the evidence presented in the medical literature, one cannot convincingly show how melanotic tumors arise primarily from the small intestines, except as the result of the aberrant displacement of cells during the early periods of body organization.

The clinical course followed in the cases of a melanoma with metastasis to the small bowel is quite interesting. One of the first points that attracts attention is the lapse of time between the removal of a mole and any evidence of metastasis to the intestinal tract. As noted above, the latent period is usually six months to two years. Such an operative history and the typical latent period were noted in the case reported above, but we cannot be sure of the type of tumor removed, although it was probably a melanoma. The signs and symptoms are not characteristic of melanomas alone but should certainly lead one to suspect a malignant process within the gastrointestinal tract. It may or may not be possible clinically to locate the tumor within the small intestine, depending on the size of the tumor, the rapidity of growth, its exact position and its effect on the lumen of the bowel. As in many cases of carcinoma of the gastrointestinal tract, the patient usually presents some history of weight loss and anorexia. Constipation or alternating constipation and diarrhea are frequent complaints. Examination of the blood often discloses a secondary anemia. When the tumor affects the second part of the duodenum, it may produce an intermittent or, later, a continuous jaundice if it involves the ampulla of Vater.

Several complications may add to these general signs and symptoms. In the first place, even though small-bowel tumors are rarely the source of bleeding in the gastrointestinal tract, they must be considered possible causes of recurrent melena.²¹ Bockus¹⁴ states that the bleeding is the most important clinical feature of carcinoma of the small intestine. Since the sarcomas tend to grow peripherally, they may not produce bleeding until late in the course of development. The tumor mass may be responsible for an intussusception, which often gives rise to an acute abdominal episode, and this acute condition is sometimes the first sign caused by the tumor. Frequently, the small-bowel tumor is first noted at the exploratory operation occasioned by such an acute condition. Fiske²² claims that 30 per cent of tumors of the small intestine cause intussusception. A chronic obstruction may be produced by the slow continuous growth of the tumor into the bowel lumen. This is more frequent in carcinoma than in sarcoma, since the former develops in the inner portion of the wall and grows centrally whereas the latter tends to grow toward the periphery. The tumor growth eventually causes perforation of the bowel wall and resulting peritonitis in rare cases.

The actual clinical diagnosis of any tumor of the small bowel is usually quite a difficult procedure and is often made on a basis of a systematic elimination of the possibilities that the lesion is in some other organ. In 38 proved cases reported by Shallow et al.¹ three quarters of the tumors were palpable, being usually fixed in the duodenum but movable in the jejunum and ileum. Sarcomas may be palpated frequently, since they tend to produce irregularity of the serosal surface of the bowel during centrifugal growth. Repeated examination of the stool for occult blood is valuable. Only about 25 per cent of the tumors can be seen on x-ray examination.² Bockus,¹⁴ however, claims that the duodenal carcinomas that are large enough to produce clinical symptoms are usually demonstrable by x-ray study and that in the diagnosis of tumors of the small intestine "progress meal x-ray examination is the only decisive diagnostic method."

The prognosis for patients with carcinoma of the small intestine is quite poor because of the delayed diagnosis and the late surgical removal of the tumor mass. McDougal²³ estimates that 5 per cent of cases reach the stage of five-year cure. Recur-

rences of the tumor in the same region or torrents of metastases may carry these few remaining victims away in later years.

SUMMARY

General statistics and a broad comparative survey of malignant tumors of the small bowel are presented and the infrequency of melanomas in the small intestine is stressed. A case of melanocarcinoma with metastasis to the ileum and brain is presented.

The sites of origin and the methods and order of metastasis are discussed. The possibility of primary melanoma of the small bowel is considered.

The clinical picture of cancer of the small intestine is briefly described.

REFERENCES

- Shallow, T. A., Eger, S. A., and Carty, J. B. Primary malignant disease of small intestine. *Am J Surg* 69:372-383, 1945.
- Boman, P. G. Primary carcinoma of jejunum and ileum. *Ann Int Med* 20:779-788, 1944.
- Bonar, A. A. Argentaffin (carcinoid) tumours of small intestine. *Brit M J* 1:391, 1946.
- Watz, C. E. Multiple malignant argentaffin (or carcinoid) tumors of small bowel with disseminated metastases. *Minnesota Med* 28:558, 1945.
- Blumgren, J. E. Malignant carcinoid tumors of small intestine: report of two cases. *Minnesota Med* 27:620-623, 1944.
- Pennington, R. E., and Priestley, J. T. Multiple carcinoid tumors of small intestine: report of case. *Proc Staff Meet, Mayo Clin* 18:49-51, 1943.
- Herbut, P. A., and Manges, W. E. Melanoma of small intestine. *Arch Path* 39:22-27, 1945.
- Ewing, J. *Neoplastic Disease: A treatise on tumors*. Fourth edition. 1160 pp. Philadelphia: W. B. Saunders Company, 1940. Pp. 721-726.
- Fraser, K. Malignant tumours of small intestine: review of literature and report of twenty-one cases. *Brit J Surg* 32:479-491, 1945.
- Rankin, F. W., and Mayo, C. J. Carcinoma of small bowel. *Surg., Gynec & Obst* 50:939-947, 1930.
- Swan, J. M. Cancer of small intestine. I. *M Times, New York* 74:46-52, 1946.
- Idem. Cancer of small intestine. II. *M Times, New York* 74:105-112, 1946.
- Eger, S. A. Primary malignant disease of duodenum. *Arch Surg* 27:1087-1108, 1933.
- Bockus, H. L. *Gastro-Enterology*. Vol. 2. Philadelphia: W. B. Saunders Company, 1943. Pp. 134-142.
- Warren, R. F. Primary malignant tumours of small bowel (review of twenty-six cases from Toronto General Hospital). *Canad M A J* 51:450-457, 1944.
- Mayo, C. W., and Nettrour, W. S. Carcinoma of jejunum. *Surg., Gynec & Obst* 65:303-309, 1937.
- Howes, W. E., and Birnkrant, M. Melanoma: review of thirty-two cases admitted to Brooklyn Cancer Institute during five year period. *Am J Surg* 60:182-189, 1943.
- DeCholnoky, T. Malignant melanoma: clinical study of one hundred seventeen cases. *Ann Surg* 113:392-410, 1941.
- Greenblatt, R. B., Pund, E. R., and Bernard, G. T. Benign nevus malignant melanoma: problem of borderline case. *South M J* 29:122-129, 1936.
- Laidlaw, G. F. Melanoma studies: dopa reaction in general pathology. *Am J Path* 8:477-490, 1932.
- Smith, L. A., Good, C. A., and Gray, H. K. Tumor of small intestine as cause of recurrent melena: report of two cases. *Proc Staff Meet, Mayo Clin* 19:117-122, 1944.
- Fiske, F. A. Intussusception due to intestinal tumors. *Ann Surg* 106:221-229, 1937.
- McDougal, W. J. Carcinoma of small intestine. *Am J Surg* 66:119-122, 1944.

MEDICAL PROGRESS

GENERAL ANESTHESIA*

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THE purpose of this paper is to summarize the progress in general anesthesia since the publication of a similar report in 1943.¹ The subject is presented under the following headings: the development of anesthesiology as a specialty, the growing importance of curare, the expanded usefulness of Pentothal Sodium, new technics and physiologic investigations.

DEVELOPMENT OF THE SPECIALTY OF ANESTHESIOLOGY

At this writing, there are approximately three hundred physicians certified by the American Board of Anesthesiology in the United States, and there are over two thousand members of the American Society of Anesthesiologists. Yet the current *News Letter* of the Society lists sixty-three vacant staff positions, as well as one hundred and two residencies or fellowships available in this specialty. The war's end has obviously left the country with an acute shortage of men trained in anesthesiology.

The great shuffling of the medical and surgical population caused by the war may have been partly responsible for a greater interest in anesthesiology. Many surgeons in the armed forces encountered either the best or the worst in anesthesia and, in either event, returned to civilian life appreciating the need for trained anesthesiologists. Mousel et al.² have analyzed the situation statistically as follows:

In the long development of surgery, even the inferior fringes of this specialty have so nearly caught up with the leaders that their gross mortality is only two to three times as great. The fact that in the relatively young specialty of anesthesiology the ratio of worst to best is represented by the ratio of more than 20 illustrates how terribly wide is the gap between what is now being given on our best services and what is being suffered on the worst or even average ones.

The wide variation between the best and average anesthetic practice calls not only for more trained anesthesiologists but also for continued concentrated effort on the part of organized anesthesiologists to raise the standard generally. Establishment of the American Board of Anesthesiology in 1938 was an important step in the progress of anesthesia. This board has done and is doing a splendid job in setting up standards for certification of specialists in anes-

esthesiology and examination of candidates for certification in this specialty.

Evidence of further progress is reflected in the increased demand and the expansion of facilities for postgraduate training in anesthesiology.

Perhaps in no other specialty does the demand for trained physicians so exceed the supply. Furthermore, it is doubtful if any other specialty has been subject to more abuse and exploitation resulting in lower quality of service to the patient. Anesthetists frequently have not been accorded proper recognition, financially or otherwise, for the important part they play in the care of patients. They have resented being relegated to the position of a technician. Yet far too often they have been content to be only technicians and have not been willing to equip themselves to assume the role of a real consultant who not only can carry out a skillful, technical procedure but also, by virtue of a background of fundamental knowledge of physiology, pharmacology and even medicine and surgery, can render a valuable opinion as a consultant.

On the other hand, surgeons have been prone to be content with anesthetic service that is not only short of the best but even short of mediocre. They have failed to realize the value of the proper anesthetic management of patients in the lowering of mortality and morbidity rates. This attitude has frequently resulted in either a conscious or unconscious exploitation of the anesthetist and also of the patient. Furthermore, it has tended to discourage younger physicians from entering this specialty. Improvement in these conditions is evidenced by the fact that there is an increased demand for trained anesthesiologists as well as for training facilities in this specialty.

Waters³ has aptly called attention to the necessity of ridding "ourselves of the generally held belief that the importance of anesthesiology lies in the choice of agents or in the particular technic employed." He calls attention to the fact that through fundamental knowledge and diagnostic skill, quite as much as through artful technical manipulation, the abuses to which all drugs and methods are subject may be either voided or neutralized.

The specialty of anesthesiology may now be practiced by the inadequately trained person neither more ethically nor more responsibly than surgery itself.

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THE DEVELOPMENT OF CURARE

Perhaps the most significant drug to be introduced into the field of anesthesia during the past four years is curare

The advantages of curare have been emphasized by many writers⁴⁻⁷ Brody,⁸ describing a technic in which curare is combined with Pentothal and nitrous oxide, observes that upper abdominal operations, "undertaken only with great difficulty and poor relaxation without curare can now be done with excellent relaxation" The total dose of Pentothal is reduced, and the postanesthetic period of depression considerably shortened Potent anesthetic agents may be given in light concentrations, and weak agents may be used for operations requiring maximal relaxation

Although Sir Walter Raleigh described curare to Elizabethan England, only after Gill's⁹ scientific missionary work were investigators presented with a constant supply of raw material that could be standardized Before Gill's experiments culminating in the period 1938 to 1940, there were three main crude preparations emerging from the South American jungles These were tubo-curare, pot-curare and calabash curare, the ingredients depending on the whim of witch doctors or up-river traders As might have been expected of these variable arrow poisons, the century of clinical and laboratory work that preceded Gill led to no accepted therapeutic technics At present, there are two standardized preparations, one more refined than the other Their action is predictable on the basis of a precise bioassay method Intocostin,* the first preparation of curare commercially available, contains 20 mg per cubic centimeter of a highly refined substance, d-Tubocurarine, the second, contains 3 mg per cubic centimeter of crystalline curare and is volumetrically equivalent in strength to Intocostin Tubocurarine is undergoing extensive clinical trial

Curare blocks the response to the nicotinic action of acetylcholine¹⁰ It prevents the effector substance at the myoneural junction of voluntary muscle from responding to the action of acetylcholine The drug also stops the synaptic transmission of impulses between preganglionic and postganglionic fibers of the autonomic nervous system

Clinically, curare causes a progressive selective paralysis and relaxation of the muscles of the head, neck, extremities, abdomen, thorax and diaphragm Good abdominal relaxation is possible without significant depression of respiratory activity Should respiratory paralysis follow an overdose, the effect is transient Complete recovery of function follows a few minutes of intelligent, forced ventilation Most authorities mention prostigmine as the physiologic antidote, but few have had occasion to use it¹⁰

Evidently curare is in part destroyed by the liver and in part eliminated unchanged in the urine

Liver or kidney damage does not, however, prolong or intensify the action Cole⁶ regards impaired renal function as a "relative contraindication"

Cole¹¹ has established that the lethal dose of curare in dogs in the presence of artificial respiration is twenty times the dose producing death by asphyxia from untreated respiratory paralysis Although the mechanism of death in the former instance is not explained, this would be valuable information, for there is no report of any pathologic effects when curare is given to a well oxygenated, anesthetized patient

Comroe and Dripps¹² have reported a histamine-like action of curare in certain patients that produces bronchoconstriction and hypotension Whitacre and Fisher⁵ mention the danger of bronchoconstriction and excessive tenacious salivation in some curarized patients who are too lightly anesthetized, increased depth or more curare will cure these effects Cullen¹⁰ writes that atropine or scopolamine premedication prevents salivation Griffith⁷ found no such need in his series

Loss of consciousness is said to occur with large doses of curare, but the prolonged period of recovery with forced respiration makes surgery under curare alone impracticable⁵ Moreover, the curarized, unanesthetized patient, if conscious, is fully sensitive to pain even when he is unable to respond Curare has no analgesic effect

Many technics for the administration of curare have been proposed^{4-8, 10, 12} The drug has been used with almost all general anesthetic agents After induction the rapid intravenous injection of an average initial dose for an adult of 3 to 5 cc of curare about the time the skin is incised usually produces maximal relaxation as the peritoneum is opened One or more doses are added intravenously as needed every twenty to thirty minutes for relaxation Ether has a curariform action, and if curare is combined with this agent, smaller doses—about a third—should be used and they must be given with extreme caution A high concentration of curare in a Pentothal solution may precipitate, thus if the two solutions are mixed, there should be an excess of Pentothal

Apart from its value in producing surgical relaxation, curare has been used successfully in the treatment of ether convulsions,¹⁴ laryngospasm⁶ and hiccups It is extremely valuable in the instrumentation or intubation of the pharynx, larynx and trachea

Curare must never be given in the absence of adequately trained personnel and the necessary equipment to provide oxygen for an otherwise helpless patient

THE EXPANDED USEFULNESS OF PENTOTHAL

In 1945 Adams¹⁵ reported the results of the first ten years of administration of Pentothal anesthesia His claims then, and more recently at the Morton

*Obtainable from E. R. Squibb and Sons, New York City

Centennial Celebration in Boston, have been remarkably conservative. He considers Pentothal extremely significant in its supplemental or integrating effect with other agents but of secondary importance when used alone. Many authors, however, report the use of Pentothal as the sole anesthetic agent for almost every conceivable operative procedure. A series of 837 cases in which major elective operations were performed under Pentothal and 100 per cent oxygen included procedures on the gall bladder and common duct in 92, gastric resections in 4 and abdominoperineal resections in 2.¹⁶ The author claims no anesthetic deaths, and only 1.8 per cent major and minor complications. Certainly, this record is beyond the experience of most anesthesiologists. Holly¹⁷ also used Pentothal in a wide variety of cases. He has found, in disagreement with Adams and most other observers, that there is no contraindication in children or even in infants.¹⁸

The abundance of Pentothal technics reported prevents any attempt to list them all even briefly. Some of the articles cover bronchoscopy,¹⁹ goiter surgery,²⁰ tonsillectomy²¹ and oral surgery.²²

There is a trend toward the use of dilute Pentothal solutions in continuous drip.²⁴⁻²⁶ The advantages claimed for this technic are smoother induction and maintenance, less danger of needle blockage, less wastage, less danger of extravasation of concentrated solution and more mechanical freedom for the anesthetist. The disadvantages are slower increase in depth, danger of overdosage and more cumbersome apparatus.

A 20-cc, 30-cc or 50-cc syringe with tubing, adapter, needle and a stopcock to prevent backflow comprises the usual equipment for administering Pentothal. For continuous-flow technics, the Pentothal is manufactured in bulk in 0.25 to 1.0 per cent solution in 5 per cent dextrose and given intravenously at a speed commensurate with the needs of the patient. The bulk solution, if backflows and other contamination are prevented, will keep at least a week at room temperature and will save considerable waste involved in the serial-injection technics. Pentothal solutions should not be used if any precipitate is present. Methods of reducing the dose of Pentothal to lighten the immediate depressant effects, as well as to shorten the postoperative recovery period, are a combination with regional block,^{26,27} local or nitrous oxide anesthesia,²⁷ use of curare or intravenous morphine^{27,28} and cocaineization of the larynx and pharynx.²¹

The contraindications to Pentothal are gradually changing. Shock is no longer an absolute contraindication.^{15,26} Rovenstine et al.^{29,30} have given Pentothal an intermediate place in the anesthesia of shock, with cyclopropane rated "good" and ether "poor." Liver damage, along with kidney damage, has been questioned as an absolute contraindication. Neither the liver nor the kidneys play a primary role in the breakdown of Pentothal.^{31,32} Holly¹⁸ has

invaded the field of pediatric anesthesia with Pentothal and is quite satisfied. The only remaining absolute contraindication to the use of the drug is inability of the anesthetist to maintain concurrently the necessary oxygenation of the patient and the desired depth of anesthesia.

NEW TECHNIQS

Various combinations of curare with inhalation anesthetics,^{13,33} or with Pentothal,⁵ constitute the basis for most of the new technics of general anesthesia. Hathaway and his associates,¹³ for example, have used curare to produce apnea and have maintained unconsciousness with nitrous oxide and oxygen during long periods of controlled respiration.

The new technics depend heavily for their success and safety on the ability of the anesthetist who has, in Drinker's³⁴ words, "had the temerity to become the oxygen supplier of another individual."

From time to time, minor improvements in equipment have appeared, such as vinyl-plastic endotracheal tubes,³⁵ new laryngoscope designs,³⁶ means of bilateral nasoendotracheal administration³⁷ and constant suction for chest surgery.³⁸ These improvements, although collectively important, are so numerous that they must be left to the process of casual discovery.

In most anesthetic procedures success is ensured by proper premedication. Driggs³⁹ has given an over-all view of the rationale. He has analyzed the effects of morphine, the barbiturates and the pressor drugs and has compared scopolamine with atropine.

Premedication is made more flexible by administration in divided doses and by the use of intravenous morphine and atropine. The maximal respiratory depressant effect following the intravenous injection of morphine is obtained in three to seven minutes.⁴⁰ Pearman²⁵ has described a safe technic and commented on the reduced amount of Pentothal following proper use of morphine. Various substitutes for morphine have been suggested to lessen postoperative nausea and vomiting.⁴¹ Handley and Ensberg,⁴² in a study of five respiratory stimulants, report amphetamine to be the most effective in combating respiratory depression following morphine overdosage.

Atropine in large doses — 0.6 mg (1/100 gr) for adults — has been suggested for prophylaxis against laryngospasm.⁴³

Atropine, but not scopolamine, counteracts the barbiturate and morphine effect of lowering the prothrombin time.⁴⁴ These findings have suggestive importance in the prophylaxis of postoperative thrombus formation.

In oral surgery the desirability of complete topical anesthesia of the pharynx and larynx has been emphasized, and the technic described.^{22,23,45}

PHYSIOLOGIC INVESTIGATIONS

Much physiologic research is of direct significance to anesthesiologists. Of this work, however, only a

small fraction — that described in the literature on surgery and anesthesia — is considered below. Even this must be in the form of suggestions for further reading rather than full discussion.

Anoxia

There are still those who condone degrees of anoxia in conjunction with nitrous oxide anesthesia.⁴⁶⁻⁴⁷ This attitude is not shared by most workers,⁴⁸⁻⁵² and the tendency in recent years is to bring the greatest enemy, anoxia, into the open. In their challenging paper, Barach and Rovenstine⁵² review disapprovingly the literature advocating so-called "asphyxia" as an adjunct to nitrous oxide administration and present factual evidence of the death and injury caused by such anoxia. Finally, they protest against the continued use of anesthetic mixtures containing less than 20 per cent oxygen.

Adams et al.⁴⁸ have made interesting measurements of blood oxygen to show that whereas the patient may be well oxygenated during operation, the oxygen concentration may fall to dangerous levels post-operatively. They also point out that high concentrations of oxygen in the anesthetic mixture do not necessarily ensure proper oxygenation, and they have analyzed at length the hindrances to proper oxygenation during intrathoracic operations. These are decreased efficiency of respiratory effect, decreased ventilation of the lung, decreased cardiac output and alteration of the transport mediums.

The work of Courville⁵³ should be read for an understanding of the pathological background to the present attack on anoxia.

Anesthesia of Shock

For the patient who is undergoing severe hemorrhage or who is in shock, cyclopropane is considered by some to be the best general anesthetic agent.²⁸⁻³⁰ After extensive microscopical observations in vivo of the peripheral circulation Rovenstine and his co-workers³⁰ have come to several valuable conclusions. "Ether anesthesia predisposed animals to early and extensive deterioration of the peripheral compensatory mechanisms and decreased their tolerance to hemorrhage and their response to transfusion. Cyclopropane did not produce these effects." They believe that cyclopropane actually improves the condition of many patients following sudden severe hemorrhage.²⁹ Evans,²⁸ although granting that cyclopropane is ideal when available, has properly insisted that other safe technics should be at hand. He has suggested regional block anesthesia and light doses of Pentothal. Gould⁴⁹ apparently still favors ether in many cases. Whatever method is used, massive intravenous therapy, — usually with blood, — minimal amounts of anesthetic, minor surgical procedures and a high concentration of oxygen are essential to success in the anesthesia of shock.

Organization of Intravenous Therapy

Intravenous therapy with particular reference to the surgical patient should be a part of the specialized knowledge of the anesthesiologist. It is a major factor in the prophylactic treatment of surgical shock. New progress has been made in the organization within the hospital for the effective and safe administration of intravenous fluids.⁵⁴

In some hospitals the entire transfusion service has become a function of the anesthesiology department.⁵⁵ In others fluid therapy, including transfusion, is the sole responsibility of the anesthesiologist in the operating room. These responsibilities, complete or limited as they may be, carry with them the need for thorough understanding of a broad physiologic field. A knowledge of the principles of blood grouping and the management of transfusion reactions, as well as an appreciation of water and electrolyte balance and protein requirements, is a prerequisite for the modern anesthesiologist.⁵⁶⁻⁵⁸

Pulmonary Edema and Inflammation

The mechanism and treatment of pulmonary edema have been described in a classic monograph by Drinker.³¹ He has explained on an experimental basis how pulmonary edema is the result of two factors: a sustained increase in the intracapillary pressure of the lungs and a decrease in the oxygen tension of alveolar air.

Early or prophylactic treatment is best. This consists in the administration of 100 per cent oxygen under a positive pressure equivalent to about 10 mm of mercury during both phases of respiration.

Increased Intrapulmonary Pressure

The widespread use of anesthetic technics and therapeutic measures, such as that suggested by Drinker, under increased intrapulmonary pressure has stimulated experimental work on the physiologic effects of such pressure. Beecher et al.⁵⁹ have stated that in animals with poor circulation increased pressure in the airway is deleterious and causes death. On the other hand, Thornton and his associates⁶⁰ have observed that it is of highest importance to the oxygenation of dogs with chest open to maintain a constant endobronchial pressure equivalent to about 8 cm of water. Knoefel et al.⁶¹ have shown that the respiration of dogs under barbitol anesthesia for three hours at a positive pressure equivalent to 7 mm of mercury leads to a 41 per cent reduction of cardiac output, with increased venous pressure and unchanged respiratory volume, oxygen consumption, blood carbon dioxide content and plasma volume. Dogs under similar conditions for one hour may or may not show reduced cardiac output. Further work on this subject is necessary. The investigations of Drinker on pulmonary edema may furnish some valuable clues.

Effect of Ether on the Lower Respiratory Tract

Surprising inferences have been drawn concerning the effect of ether on the output of fluids by the lower respiratory tract.⁶² No change in such secretion was found in the first through the third plane of anesthesia in etherized dogs, cats and rabbits. In addition, since postural drainage did not increase the apparent flow, the conclusion was reached that ciliary action in the lower respiratory tract is not altered by inhaled ether. Atropine sulfate also has no effect in decreasing fluid production in this region. These findings, if corroborated in man, increase the importance of the role of upper-respiratory-tract secretion in the etiology of atelectasis, and cuffed endotracheal tubes may be more frequently indicated.

Atelectasis

A group of simple experiments by Hilding⁶³ have given a probable explanation of the mechanism of atelectasis. In a cylinder of hen trachea considerable negative pressure builds up behind piston-like mucous material moved orally by ciliary action. It is suggested that this piston-like action, and not the absorption of gases trapped behind fixed mucous plugs, is the principal factor producing collapse of distal lung segments.

Laryngospasm

Annoying and frequently dangerous reflexes producing laryngospasm are only moderately well controlled by heavy doses of atropine.⁶⁴ Moreover, once laryngospasm is most frequently encountered during light anesthesia, vomiting and aspiration may precipitate a crisis. A reliable, rapidly acting means of controlling the spasm has been widely sought. Curare is said by some to offer an effective solution.⁶⁵

Effect of New Drugs

The group of drugs represented by propyl thiouracil has reduced the problems of anesthesia for thyroid surgery essentially to those for any other surgical procedure about the neck. With almost no exception, thyroid storms and the heavy doses of anesthetic agents necessary in thyrotoxicosis are part of medical history.

Another group of drugs, represented by penicillin and streptomycin, have reduced postanesthetic morbidity and mortality.

Ether Convulsions

Rosenow, Mousel and Lundv⁶⁶ have reported further investigation in an attempt to establish an etiologic relation between certain streptococci and convulsions under ether anesthesia.

Cyclopropane Arrhythmias

Since the introduction of cyclopropane, two constant objections have plagued the administrator: an

extremely real explosion hazard⁶⁶⁻⁶⁷ and the occurrence of dangerous cardiac arrhythmias.⁶⁸ The explosion hazard has been reduced by the proper training of operating-room personnel, the elimination of materials and machines producing high charges of static electricity, the use of closed technics, the use of the Horton intercoupler and other more debatable measures.⁶⁹

The arrhythmias remain as part of the calculated risk present with this, as it is with any other, anesthetic agent. They vary from premonitory sinus arrhythmia, dropped beats and coupled beats to ventricular fibrillation and cardiac standstill.

Direct cardiac massage and forced respiration are the principal factors in resuscitation.⁷⁰ Recent work by Stutzman et al.⁷¹ indicates that intravenous procaine has no value in restoring normal rhythm once ventricular fibrillation has occurred. Burstein and his associates,⁷²⁻⁷⁴ however, who carried out the original work on the use of procaine, have since presented case reports⁷⁵ to refute the animal experiments of Stutzman. Burstein has used intravenous procaine for cardiac arrhythmias during anesthesia in dosages of 3 to 7 cc of a 1 per cent solution.

Allen et al.⁷⁶ investigated the mechanism of cardiac arrhythmias in cats under cyclopropane anesthesia and decided that, whereas vagal tonus is not essential in the mechanism, cardiac sympathectomy abolishes spontaneous cyclopropane arrhythmias of ventricular origin. They have discussed the danger of sympatheticolytic drugs in practice, however, and have advised dilution of cyclopropane with more oxygen at the onset of cardiac arrhythmias. If this measure is not effective or if the proper level of anesthesia cannot be maintained, they have used a different agent.

Explosion Hazards

The danger of anesthetic explosion has been discussed,⁶⁶⁻⁶⁷ but only one new preventive suggestion has been put forth — the ionization of the air to reduce static electricity accumulations.⁶⁹ This measure appears to be less practicable than the program set forth in the report of the Committee on Static Electricity,⁷⁷ reprinted from the *Quarterly of the National Fire Protective Association*.

Chemical Absorbents of Carbon Dioxide

Following laboratory experiments, Adriani⁷⁸ fixed the ideal characteristics of agents used to absorb carbon dioxide during anesthesia. The optimum water content (between 10 and 22 per cent),⁷⁹ the size of granules (4 to 8 mesh) and other mechanical and chemical variables have been summarized in his new book.⁸⁰ More recently, Mousel, Weiss and Gilliom,⁸¹ after extensive clinical investigation, have favored baralyme as a more satisfactory absorbent for general use.

Electronarcosis

The production of the anesthetic state by electric currents has been known for decades. The method is relatively safe and reversible in the effects noted. Although the phenomenon is still under investigation, it is not yet suited for clinical application.^{82, 83}

Metopryl

The most recent efforts of the Krantz⁸⁴ group to replace ether have resulted in a product called Metopryl. This volatile agent, closely related to di-ethyl ether, was recently proposed, at a meeting of the International College of Anesthetists, as an agent surpassing ether in rapidity of action, freedom from local irritation and surgical relaxation. Confirmation from other workers has not yet been given.

REFERENCES

- Zentgraf, L. P., and Eversole U. H. General anesthesia. *New Eng J Med* 229 437-441, 1943.
- Mousel, L. H., Stubbs, D., and Kreiselman, J. Anesthetic complications and their management. *Anesthesiology* 7 69-79, 1946.
- Waters, R. M. Anesthesiology in hospital and in medical schools. *J A M A* 130 909-912, 1946.
- Cullen, S. C. Use of curare for improvement of abdominal muscle relaxation during inhalation anesthesia: report on 131 cases. *Surgery* 14 261-266, 1943.
- Whitacre, R. J., and Fisher, A. J. Clinical observations on use of curare in anesthesia. *Anesthesiology* 6 124-130, 1945.
- Cole, F. Use of curare in anesthesia: review of 100 cases. *Anesthesiology* 6 48-56, 1945.
- Griffith, H. R. Curare in anesthesia. *J A M A* 127 642-644, 1945.
- Brody, J. Use of curare in sodium pentothal-nitrous oxide-oxygen anesthesia. *Anesthesiology* 6 381-384, 1945.
- Gill, R. C. Curare: misconceptions regarding discovery and development of present form of drug. *Anesthesiology* 7 14-23, 1946.
- Cullen, S. C. Clinical and laboratory observations on use of curare during inhalation anesthesia. *Anesthesiology* 5 166-173, 1944.
- Cole, F. New lethal dose of curare with some observations on pathology produced by large doses. *Anesthesiology* 7 190-197, 1946.
- Comroe, J. H., Jr., and Dripps, R. D. Histamine-like action of curare and tubocurarine injected intracutaneously and intra arterially in man. *Anesthesiology* 7 260-262, 1946.
- Harroun, P., Beckert, F. E., and Hathaway, H. R. Curare and nitrous oxide anesthesia for lengthy operations. *Anesthesiology* 7 24-28, 1946.
- Greenfield, I. Convulsions during ether anesthesia controlled by curare (Intocostin). *Anesthesiology* 7 299-301, 1946.
- Adams, R. C. Pentothal sodium intravenous anesthesia in peace and war. *J A M A* 126 282-287, 1944.
- French, E. A. Pentothal sodium oxygen anesthesia in major surgery. *Am J Surg* 61 16-37, 1943.
- Holly, J. D. Pentothal sodium in major surgical procedures. *Am J Surg* 62 13-18, 1943.
- Idem*. Intravenous anesthesia in children. *South M J* 37 631-637, 1944.
- Fatti, L., and Morton, H. J. V. Pentothal anesthesia in bronchoscopy. *Lancet* 1 597, 1944.
- Hudon, F. Four hundred ten cases of goiter under general anesthesia with pentothal. *Anesth & Analg* 23 211-214, 1944.
- Fox, S. L., and Rochberg, S. Anesthesia for tonsillectomy induced by intravenous administration of pentothal sodium. *Arch Otolaryng* 41 439, 1945.
- Elliot, H. L., and Arrowood, J. G. Anesthesia for oral surgery in presence of cautery and diathermy. *Anesthesiology* 6 32-38, 1945.
- Roche, G. K. T. Anesthesia of recent injuries of jaw and face. *Anesthesiology* 7 233-254, 1946.
- Narat, J. K., and Giraldo, E. Intravenous anesthesia in major surgery: use of one per cent solution of pentothal sodium. *Am J Surg* 66 178-181, 1944.
- Stevens, E. J. Pentothal sodium: its use in continuous intravenous anesthesia and method of preserving it in solution. *Anesthesiology* 6 376-380, 1945.
- Evans, E. I. Studies on traumatic shock: anesthesia in clinical shock. *J A M A* 124 473-478, 1944.
- Damarian, E. Pentothal anesthesia. *Anesthesiology* 6 402-409, 1945.
- Pearman, R. O. Intravenous use of morphine sulfate. *Am J Surg* 61 423, 1943.
- Hershey, S. G., and Rovenstine, E. A. Value of cyclopropane in anesthetic management of patients with recent severe hemorrhage. *Anesthesiology* 5 149-158, 1944.
- Hershey, S. G., Zweifach, B. W., Chambers, R., and Rovenstine, E. A. Peripheral circulatory reactions as basis for evaluating anesthetic agents. *Anesthesiology* 6 362-375, 1945.
- Mason, G., and Beland, E. Influence of liver and kidney on duration of anesthesia produced by barbiturates. *Anesthesiology* 6 483-491, 1945.
- Scheiffel, C. H. Pentothal sodium: its use in presence of hepatic disease. *Anesthesiology* 7 263-267, 1946.
- Holaday, D. A. Nitrous oxide-cyclopropane-curare anesthesia: review of 200 cases. *Anesthesiology* 7 426-440, 1946.
- Drinker, C. K. Pulmonary edema and inflammation. An analysis of processes involved in formation and removal of pulmonary transudates and exudates. 106 pp. Cambridge: Harvard University Press, 1945.
- Gordon, R. A., and Ainslie, E. H. Experience with vinyl-plastic endotracheal tubes. *Anesthesiology* 6 359-361, 1945.
- Wiggin, S. C. New modification of conventional laryngoscope and technique for laryngoscopy. *Anesthesiology* 5 61-68, 1944.
- Gordon, R. A. Bilateral nasotracheal intubation for closed system anesthesia. *Anesthesiology* 5 186-191, 1944.
- Pinson, K. B., and Graham Bryce, A. Constant suction in thoracic surgery: description of anesthetic apparatus. *Brit J Anaesth* 19 53-61, 1944.
- Dripps, R. D., Jr. Pharmacologic basis for preoperative medication. *S Clin North America* 24 1377-1388, 1944.
- Dripps, R. D., and Comroe, J. H., Jr. Clinical studies on morphine effect of morphine administered intravenously and intramuscularly upon respiration of normal man. *Anesthesiology* 6 462-468, 1945.
- Steele, J. D. Narcotic as factor in postoperative nausea and vomiting. *Anesthesiology* 4 430-432, 1943.
- Handley, C. A., and Ensberg, D. L. Comparison of amphetamine sulfate with other stimulants of the central nervous system in morphine respiratory depression. *Anesthesiology* 6 561-564, 1945.
- Drill, W. W. Laryngospasm and premedication. *Anesth & Analg* 22 233-235, 1943.
- Levy, S., and Conroy, L. Prothrombin time and anesthesia: clinical investigation on effects of ether and spinal anesthesia on prothrombin level of blood. *Anesthesiology* 7 276-284, 1946.
- Dietrich, W. C., and Beutner, R. Search for least irritant topical anesthetic. *Anesthesiology* 7 255-259, 1946.
- Waters, R. M. Relation of anesthesia to hypoxia and anoxia. *J A M A* 126 1068, 1944.
- Conroy, W. A. Analgesia and anesthesia for obstetrics: inhalator methods. *Am J Obst & Gynec* 48 81-84, 1944.
- Adams, W. E., Thornton, T. F., Jr., Carlson, A. J., and Livingstone, H. M. Ethylene anoxia and anesthesia in intrathoracic operations: clinical study. *Surgery* 13 859-879, 1943.
- Gould, R. B. Anesthesia for patient in shock. *Anesthesiology* 5 129-141, 1944.
- Heard, K. M. Benefits and hazards of pentothal anesthesia. *Anesthesiology* 5 448-464, 1944.
- Maier, H. C. Responsibility of the anesthetist in reducing operative complications of thoracic surgery. *Anesthesiology* 5 11-21, 1944.
- Barach, A. L., and Rovenstine, E. A. Hazard of anoxia during nitrous oxide anesthesia. *Anesthesiology* 6 449-461, 1945.
- Courville, C. B. Asphyxia as consequence of nitrous oxide anesthesia. *Medicine* 15 129-245, 1936.
- Seldon, T. H., Lundy, J. S., and Adams, R. C. Blood transfusion: service dangers and safeguards. *Anesthesiology* 7 122-131, 1946.
- Idem*. Transfusions of blood and plasma. *Anesthesiology* 5 22-31, 1944.
- Collins, C. C., Jr., and Nicholson, M. J. Rh factor. *Anesthesiology* 5 254-261, 1944.
- Bradaach, G. A. Comparative value of various parenteral fluids. *Anesthesiology* 5 1-10, 1944.
- Drew, C. R. Early recognition and treatment of shock. *Anesthesiology* 3 176-194, 1942.
- Beecher, H. K., Bennett, H. S., and Bassett, D. L. Circulatory effect of increased pressure in airway. *Anesthesiology* 4 612-618, 1943.
- Thornton, T. F., Jr., Martin, R. C., Livingstone, H. M., and Adams, W. E. Effect of variations of intratracheal pressure and anesthetic mixtures on arterial blood oxygen (experimental study). *Anesthesiology* 6 498-504, 1945.
- Knoefel, P. K., Holt, J. P., Quinn, C., Ambrose, A. M., and Shore, F. Some effects of positive pressure respiration during anesthesia. *Anesthesiology* 6 349-354, 1945.
- Boyd, E. M., and Munro, J. S. Ether anesthesia and output of fluids from respiratory tract. *J Pharmacol & Exper Therap* 71 346-353, 1943.
- Hilding, A. C. Production of negative pressure in respiratory tract and its relation to postoperative atelectasis. *Anesthesiology* 5 223-236, 1944.
- Knight, R. T. Use of curare in anesthesia. *Minnesota Med* 27 667-670, 1944.
- Rosenow, E. C., Mousel, L. H., and Lundy, J. S. Further studies on muscular spasms during general anesthesia: experimental results with neurotropic streptococci from nasopharynx of patients. *Anesthesiology* 6 12-31, 1945.
- Clark, L. H. Some dangers involved in use of anesthetics in x-ray departments. *Radiography* 10 25-27, 1944.
- Hadfield, C. F. Use of anesthetics in x-ray departments. *Radiography* 10 17-23, 1944.
- Taylor, I. B. Cyclopropane anesthesia with reports of results. 41,690 administrations. *Anesthesiology* 2 641-653, 1941.
- Slocum, H. C., and Finfold, R. Ionization of air: method for determination of static electricity. *Anesthesiology* 5 33-39, 1944.

70. Butler R. F., and Madden, J. L. Resuscitation of heart. *Am J Surg* 64:151-168 1944
71. Cummins J. W., Allen C. R. and Orth O. S. Failure of procaine to reverse cyclopropane-epinephrine ventricular fibrillation. *Anesthesiology* 17:637-640 1945
72. Burnett, C. L., Marangoni B. A., DeGraff A. C. and Rovenstone E. A. Laboratory studies on prophylaxis and treatment of ventricular fibrillation induced by epinephrine during cyclopropane anesthesia. *Anesthesiology* 1:167-186 1940
73. Burnett, C. L., and Marangoni B. A. Protecting action of procaine against ventricular fibrillation induced by epinephrine during cyclopropane anesthesia. *Proc Soc Exptl Biol & Med* 43:310-312, 1940
74. Marangoni, B. A., Burnett C. L. and Rovenstone E. A. Protecting action of chemicals related to procaine on ventricular fibrillation during cyclopropane anesthesia. *Proc Soc Exptl Biol & Med* 44:594-596 1940
75. Burnett, C. Treatment of acute arrhythmias during anesthesia by intravenous procaine. *Anesthesiology* 7:113-121 1946
76. Allen C. R., Hoefflich E. A., Cooper B. M., and Stocum H. C. Influence of autonomic nervous system upon spontaneous cardiac arrhythmias during cyclopropane anesthesia. *Anesthesiology* 6:261-267 1945
77. Report of Committee on Static Electricity. *Anesthesiology* 3:85-91 1942
78. Adams J. Soda lime containing indicators. *Anesthesiology* 5:45-52 1944
79. *Idea*. Effect of varying moisture content of soda lime upon efficiency of carbon dioxide absorption. *Anesthesiology* 6:163-172 1945
80. *Idea*. *The Chemistry of Anesthesia* 536 pp. Springfield Illinois: Charles C. Thomas 1946
81. Mouse L. H., Weiss W. A. and Gilliom L. A. Clinical study of carbon dioxide absorption during anesthesia. *Anesthesiology* 7:598 1946
82. Ross P. S. Electrocortosis. *Anesthesiology* 4:670-676 1943
83. Frosting J. P. and others. Electrocortosis in animals and in man. *Arch Neurol & Psychiat* 51:232-242 1944.
84. White, M. L. T., Shane S. M. and Kraatz, J. C. Jr. Anesthesia with isopropyl ether as inhalation anesthetic in man (preliminary report). *Anesthesiology* 7:663-667 1946

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 33221

PRESENTATION OF CASE

First admission. A forty-two-year-old housewife entered the hospital because of vaginal bleeding. The patient had been in excellent health until six months before entry, when she had first noticed slight generalized weakness and easy fatigability. Three months later an unusually prolonged and profuse period had occurred, and she had subsequently had some intermittent intermenstrual bleeding associated with abdominal cramps, gradually increasing in severity. She had also had occasional hot flashes. During the next to the last period, which occurred four weeks before entry, she used ten to fifteen napkins a day and passed some blood clots. Abdominal cramps were again severe, and she had one episode of "cold sweats" and fainting. Since then she bled almost every other day, requiring as many as ten napkins a day. Six days before entry she began to bleed constantly, passing some small clots, and on the day before entry she passed a clot about the size of a fist. During the three days before entry she occasionally had chill sensations and fainted several times. There had been no pain or headaches.

The patient had begun to menstruate at the age of sixteen years, and until the present illness the periods had always been regular, occurring every twenty-six to twenty-eight days and lasting for five or six days. They had always been somewhat

profuse. She had had six children, the eldest of whom was twenty-six years and the youngest fourteen years of age. In the two months before entry she had lost about 10 pounds. She had not had intercourse for eight months before entry.

Physical examination revealed a pale, somewhat obese woman. The heart, lungs and abdomen were normal. There was a slight cystocele and first-degree procidentia. There was a bloody discharge from the cervix. The uterus was about twice the normal size and in third-degree retroversion.

The temperature, pulse and respirations were normal. The blood pressure was 130 systolic, 70 diastolic.

Examination of the blood disclosed a red-cell count of 3,300,000, with 12.0 gm. of hemoglobin, and a white-cell count of 5400, with 60 per cent neutrophils. A blood Hinton test was negative. The urine was normal.

On the third hospital day a total hysterectomy was performed. The cervix was bilaterally ulcerated and contained some small Nabothian cysts. The uterus measured 10 by 4 by 3 cm., and the myometrium was studded with firm, yellowish-orange nodules, 1 or 2 mm. in diameter. The endometrium was reddish orange and 1 mm. thick except at the fundus, where a 1.5-cm. polypoid mass was present. The pathological diagnosis was neurofibromas of the myometrium. The patient recovered uneventfully and was discharged on the seventeenth hospital day.

Second admission (two years later). Following discharge the patient continued to complain of weakness. She also had slight stress incontinence, which was the presenting complaint. The weight had increased from 149 pounds at the time of the first admission to 158 pounds.

The physical findings were essentially unchanged. The hemoglobin was 15.0 gm., and the white-cell count 5400. The urine was normal.

On the fourth hospital day an anterior colporrhaphy and a perineorrhaphy were performed. The postoperative course was uneventful, and the patient was discharged on the fifteenth hospital day.

Third admission (fourteen months later). For several months after the operation the patient was

well and continent of urine. Then, slight incontinence returned. Also, she continued to suffer from weakness and fatigue. Iron pills prescribed by a physician were of no avail. For ten months she had had occasional attacks of nausea and cramps in the "pit of the stomach." These episodes usually came within thirty minutes to an hour following a meal. She had no intolerance to fatty foods. She also complained of increasing constipation and frequent hot flashes and jittery spells lasting about fifteen minutes at a time. She had lost about 10 pounds in weight despite progressive enlargement of the abdomen for several months.

On physical examination the patient appeared chronically ill. The lungs were clear. The abdomen was protuberant and tympanitic. Peristalsis was active. A large, poorly defined, somewhat movable, hard, slightly tender mass filled most of the right lower and middle portions of the abdomen. It was ovoid in shape, with its long axis parallel to the long axis of the body, arose in the pelvis and extended to the umbilicus. A smaller cystic mass was felt in the left pelvis, and there was a mass dissecting down between the vagina and the rectum.

The temperature was 102.5°F, the pulse 120, and the respirations 25. The blood pressure was 120 systolic, 75 diastolic.

Examination of the blood revealed a hemoglobin of 11.2 gm and a white-cell count of 15,500 with 89 per cent neutrophils. The nonprotein nitrogen was 25 mg, and the serum protein 6.7 gm per 100 cc.

The urine gave a ++ test for albumin. The sediment from a catheterized specimen contained 3 red cells and 20 white cells per high-power field. Cultures showed abundant colonies of colon bacilli.

X-ray examination disclosed an area of horizontal linear density in the left lower-lung field. There were a number of rounded, calcified areas with centers of decreased density in the right upper quadrant of the abdomen. A rounded calcified mass, 3 cm in diameter, was present in the left upper quadrant. The kidneys appeared normal in position and size, the right being slightly larger than the left. Both excreted intravenous dye promptly, and the urinary passages on the left appeared normal. There was a marked accumulation of dye in the right kidney two hours after injection and moderate dilatation of the right pelvis, calyces and upper right ureter. Both ureters were displaced laterally by what appeared to be a lobulated mass about 13 cm in diameter in the midpelvis. This compressed the upper border of the bladder. A second, rounded mass about 11 cm in diameter was lying over the upper border of the sacrum on the right. These masses were rather sharply defined, smooth and free of calcification. A barium enema showed no evidence of intrinsic bowel disease.

On the sixth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR PAUL A YOUNGE On the first admission this patient had a cystocele and a first-degree procidentia. There is often confusion between the terms "prolapse" and "procidentia" of the uterus. Procidentia, as we use the term, means that the uterus is outside the introitus.

DR FRANCIS M INGERSOLL I should say that the uterus was moderately prolapsed, it just came down to the introitus.

DR JOE V MEIGS Then this was not a procidentia.

DR YOUNGE I should say, a second-degree prolapse.

Symptoms of cramps with flowing usually mean definite intrauterine lesion, such as pedunculated fibroid or pedunculated adenomyoma. Occasionally with dysfunctional flowing, large clots are passed in association with cramps, but there is not so much intermenstrual bleeding as this patient had. From the history, I think that she had a submucous pedunculated tumor. Another lesion that could cause the symptoms is a carcinoma of the cervix obstructing the cervical canal. This results in pain and intermenstrual bleeding that is perhaps not so profuse as that in the case under discussion. I assume that dilatation and curettage were not done beforehand, since no mention is made of such procedures.

The uterus that was removed is described as measuring 10 by 4 by 3 cm, that fact fails to substantiate the clinical finding of a uterus twice the normal size because the measurements are those of a normal or somewhat small uterus. There was a small intrauterine tumor, which may have caused the symptoms of cramps and bleeding. The gross description sounds like an endometrial polyp, and I am mystified by the pathological diagnosis of neurofibroma of the myometrium. That is a completely new lesion of the uterus so far as I am concerned, and I do not know its significance. It is possible that it was a part of a generalized neurofibromatosis, but there is no confirmatory evidence for such a hypothesis in the history or the physical examination. I also fail to understand why at the first operation nothing was done about the relaxed pelvic floor.

On the third admission the outstanding symptoms were loss of weight, general debility and cramps and nausea after eating. Physical examination disclosed bilateral pelvic masses, one of which extended up into the abdomen. The intravenous pyelogram demonstrated ureteral obstruction on the right. The pelvic tumor that most frequently causes obstruction in the urinary tract is carcinoma of the cervix, and I have considered that diagnosis seriously in spite of the description of the cervix at the time of hysterectomy. The ovaries were not removed at the first operation, and bilateral pelvic tumors and gastrointestinal symptoms such as she had made

one think of a Krukenberg tumor. The ovaries may have developed a primary malignant tumor, but carcinoma of the ovary seldom causes ureteral obstruction. The patient must have had an infiltrating tumor in the broad ligament obstructing the ureter, and we know that she had infiltration of the recto-vaginal septum. This again makes one think of carcinoma of the cervix, but since that is apparently

urinary tract on the right. The barium in the small intestine outlines the soft-tissue mass.

DR YOUNG: I did not realize that there were three pelvic masses.

DR WYMAN: I do not know whether there are three or whether it is one lobulated mass.

DR YOUNG: Since one of the original lesions was a neurofibroma, I suppose that one should consider

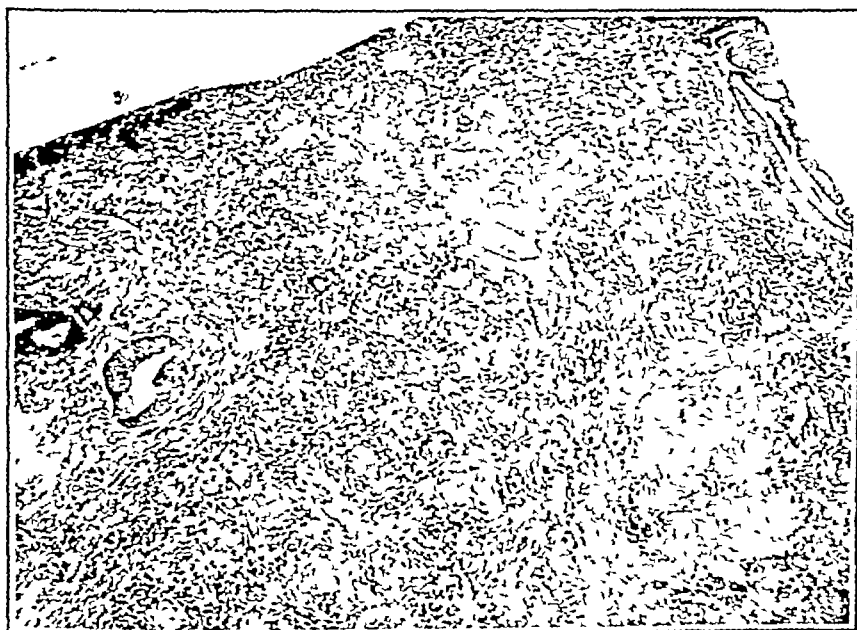


FIGURE 1

ruled out, my diagnosis is a Krukenberg tumor of the ovary, bilateral, with metastases in the pelvis causing ureteral obstruction and hydronephrosis. She also had gallstones. I am not certain what to say about the x-ray findings of the lungs—they may have been due to a thick interlobar septum and were probably not due to cancer.

DR STANLEY WYMAN: The area of linear density in the left lower-lung field just above the diaphragm. There may be some collapse of the lower lobe. I think of atelectasis. This plain film of the abdomen, taken on the same day, shows a rounded mass. A second overlying shadow is faintly discernible at this point, and a third round mass overlaps, with some gas apparently flowing around it. The small areas of calcified ringlike density that are seen in the right upper quadrant conform to the configuration of the expected site of the gall bladder. This is the mass of round calcification seen on the left. After the intravenous introduction of dye, the first film shows delay in excretion by the right kidney, presumably due to the obstructed ureter. The film taken two hours after the introduction of dye shows considerable dye remaining in the upper

neurofibrosarcoma. But I know nothing about that. I do not know what to expect benign uterine neurofibromas to be accompanied by or followed by, and I shall omit that as a possibility and stick to the diagnosis of Krukenberg tumor.

DR TRACY B. MALLORY: The diagnosis of neurofibromatosis of the uterus was made during my absence from the laboratory, and I disclaim responsibility. I do not wonder that the pathologist was puzzled by the sections, one of which is shown in Figure 1. This is from the polypoid tumor in the uterine cavity and shows a few widely dispersed endometrial glands separated by exceptionally abundant endometrial stroma. In this stroma were numerous whorls of exceptional cellularity. Similar masses of small spindle cells, also with a tendency to whorl formation, invaded deeply into the myometrium. The pattern resembles that seen in tumors arising from nerve sheaths, but I do not believe that I should have made that diagnosis. I seriously considered the possibility of a granulosa-cell tumor primary in the ovary, but the apparent normality of the ovaries at the first operation made this ex-

tremely improbable I finally decided that an endometrial sarcoma was the best diagnosis

DR YOUNGE Could you exclude leiomyosarcoma or cellular leiomyoma? We have had a recent case of so-called "cellular leiomyoma" in which the patient is dying of metastatic sarcoma. The lesion in the case under discussion may have been a sarcoma.

DR MALLORY I believe that one can rule out leiomyoma or leiomyosarcoma, since these cells are tiny spindle cells, much smaller than muscle cells.

CLINICAL DIAGNOSIS

Carcinoma of ovary?

DR YOUNGE'S DIAGNOSIS

Krukenberg tumor of ovary

ANATOMICAL DIAGNOSIS

Endometrial sarcoma?

Stromal endometriosis (endolymphatic fibromyosis of Frank)?

PATHOLOGICAL DISCUSSION

DR MALLORY Dr Ingersoll, will you tell what you found at operation?

DR INGERSOLL At operation the lower half of the abdomen was studded with a polypoid type of tumor that had infiltrated the omentum and was adherent to the abdominal wall. In the pelvis there were other masses of a similar type of tumor. It was not like any tumor that I had seen before. The omentum and other tissues seemed to be studded with smooth, round masses of varying size. We resected the omentum but were unable to remove the tumor in the pelvis.

DR MEIGS Did you remove the ovaries?

DR INGERSOLL No, the small bowel, the large bowel and everything else were adherent in the pelvis.

DR MEIGS I bring up that point for later discussion in connection with the treatment. It may be important. You did not consciously remove the ovaries?

DR INGERSOLL No.

DR MALLORY The Pathology Department worried over the diagnosis of this case once more for several weeks after the third operation. The probable clue to it, I think, was found, not in the original sections of the uterus, but in the new tumor growth of the omentum. This presented a peculiar appearance—multiple nodules of varying size, some less than a millimeter in diameter, others up to 2 or 3 cm in diameter, of a small spindle-cell neoplasm, which was projecting into and growing in the lumen of spaces lined with endothelium that seemed to be tremendously dilated lymphatic vessels. A characteristic nodule is shown in Figure 2. The tumor corresponds entirely in its histologic appearance to a group of lesions that were reported some years ago by Frank¹ at the Mount Sinai Hos-

pital under the title of "endolymphatic fibromyosis of the uterus." The same tumor has unquestionably been called by other names. I am quite sure that it has been referred to at times as stromal endometriosis, and in certain respects it suggests that

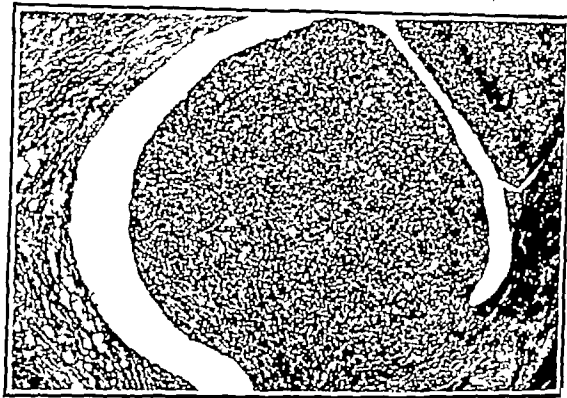


FIGURE 2

condition. We have had a case in the old records of the hospital that Dr Meigs² studied some years ago and illustrated in his book. I suggest that he say something about it.

DR MEIGS When I ran across this tumor in going over the histologic sections in the laboratory, I called it a "leiomyosarcoma invading a fibroid." Dr Goodall³ and later Dr James Miller,⁴ of Hartford, reported a stromal endometrium, having all the characteristics seen in this picture. This picture in my book, which was drawn without knowledge of what it was, demonstrates the small worm-like nodules growing in the lymphatic vessels of the fibroids. Our case was undoubtedly a stromal endometrium invading lymphatic vessels and was similar to Dr Miller's case.

May I ask Dr Ingersoll if x-ray treatment was given? In certain cases of stromal endometriosis, even though the tumor appears extremely malignant, with extensive invasion of the lymphatic vessels, x-ray treatment has been effective, presumably as the result of abolishing ovarian function. If this patient received x-ray treatment, what happened to her?

DR INGERSOLL She was extremely ill throughout her stay in the hospital, and we gave an unfavorable prognosis, not knowing what type of tumor she had. She received a total of 4100 r during a three-week period. When seen in my office four months later she looked well. All the masses have disappeared except the one in the rectovaginal septum.

DR MEIGS That is what Goodall and Miller state that x-ray treatment, not of the tumor but of the gonads, may perform the miracle that seems

to have been performed. This tumor and the one in the book are similar. My patient is also living and well, after a total removal of the genital organs. It looked as if she could not live when one saw the tumor masses, but she did.

DR INGERSOLL: One of the patients in Frank's original cases responded well to x-ray treatment. The tumor had been incompletely removed, and following operation the patient received x-ray treatment and survived for a long time.

REFERENCES

1. Frank, R. T. "Fibromyoma," unclassified plexiform endolymphatic proliferation of uterus. *Am. J. Cancer* 16: 1326-1336, 1932.
2. Merr, J. V. *Tumors of the Female Pelvic Organs*. 553 pp. New York: Macmillan Company, 1934. P. 147.
3. Goodall, J. K. Endometrioma interstutiale. *J. Obst. & Gynec. Brit. Emp.* 47: 13-39, 1940.
4. McCr, J. R., and Tennant, R. Endometriosis interstutiale with report of three cases. *Am. J. Obst. & Gynec.* 47: 784-793, 1944.

CASE 33222

PRESENTATION OF CASE

A fifty-year-old unmarried, retired schoolteacher was admitted to the hospital because of abdominal cramps and distention.

For twenty-five years the patient had had recurrent, transient gastrointestinal upsets, occurring on an average of two or three times a year and lasting two or three hours. The episodes were characterized by pain and gas in the upper abdomen, nausea, vomiting and diarrhea. About two years before entry x-ray studies — apparently, a gastrointestinal series and a barium enema — were said to have been negative. For the five months immediately preceding entry she had noticed a gradual but definite change in symptoms, with increasing, audible borborygmi and shifting "lumps of gas" in the abdomen. She had had occasional cramping periumbilical pain, with nausea and vomiting, and intermittent alternating constipation and diarrhea. She denied having noted hematemesis, tenesmus, bleeding by rectum or black, tarry stools. The stools had often been light, almost white, but she had never been jaundiced or noticed dark urine. She had had no chills or fever. Fatty foods always caused some dyspepsia. Four nights before entry she had awakened in the middle of the night with a particularly severe attack of abdominal cramps and diffuse pain. A gastrointestinal series and barium enema in another hospital revealed something "down low in the small bowel that required operation very soon." She had taken practically nothing by mouth on the day of entry and had had two small watery movements without gas. She admitted a weight loss of undetermined amount in the preceding four months.

A thyroidectomy had been performed twenty years previously. The patient stated that her mother and a maternal aunt had died of cancer and that one of her sisters was seriously ill with cancer

of the breast. One sibling had died of tuberculosis.

Physical examination revealed a thin, pale, somewhat dehydrated woman in no acute discomfort. The abdomen was distended and tympanitic. There was visible, audible and palpable peristalsis, with rushes, high-pitched tinkles and fluid gurglings of the distended loops of bowel. There was moderate tenderness without spasm in the lower abdomen in the midline, but no masses. The examination was unsatisfactory, however, because of the distention.

The temperature, pulse and respirations were normal. The blood pressure was 120 systolic, 70 diastolic.

The white-cell count was 8500, with a normal differential. The hemoglobin was 11.4 gm, and the hematocrit 36. The urine was normal. The nonprotein nitrogen was 23 mg, and the total protein 5.6 gm per 100 cc. The chloride was 101 milliequiv, and the carbon dioxide 25.4 milliequiv per liter. X-ray examination was not repeated in this hospital.

During the first week in the hospital decompression of the small-bowel distention with a Harris tube was effected. By the fifth hospital day the tube lay over the sacrum and was apparently fairly close to the point of obstruction. The patient was given 2500 to 4000 cc of intravenous fluids a day including Amigen, dextrose, physiologic saline solution and vitamins, and four transfusions were administered.

On the eighth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR ARTHUR W. ALLEN: The record states that no x-ray studies were done in this hospital. Do we have the films taken outside?

DR LAURENCE L. ROBBINS: No, but I can help you a little by describing them. I have brought along a film that shows an essentially similar appearance. Here is a single dilated loop of small bowel that appears to arch around something, as if it might partially surround a tumor mass. The dilated segment of bowel terminates with a shelf-like margin, and distal to this point the bowel is relatively collapsed. That is as close as I can come to describing the x-ray appearance. The dilated loop was demonstrated in two films taken some time apart, and its appearance remained essentially unchanged. The fluoroscopist believed that he could localize the obstruction in the lower small bowel.

DR ALLEN: I was certain that a film of the abdomen had been taken on admission so that we could see to what extent the loops of small intestine had become dilated. I suppose that without the slightest doubt we must accept the fact that she had small-bowel obstruction, which was low in the ileum.

The past history is interesting. It is difficult for me to see how we can account for the episodes of gastrointestinal difficulties lasting only two or

tremely improbable I finally decided that an endometrial sarcoma was the best diagnosis

DR YOUNGE Could you exclude leiomyosarcoma or cellular leiomyoma? We have had a recent case of so-called "cellular leiomyoma" in which the patient is dying of metastatic sarcoma. The lesion in the case under discussion may have been a sarcoma.

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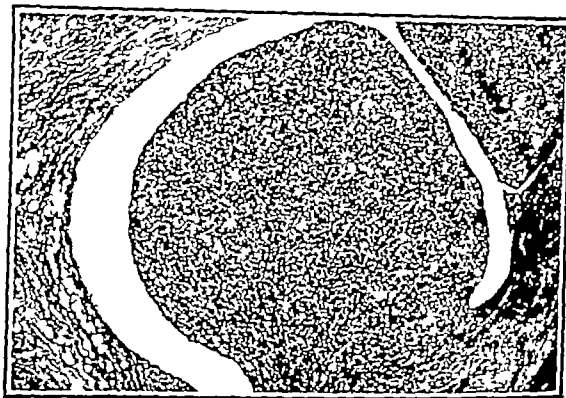


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DR MEIGS That is what Goodall and Miller state that x-ray treatment, not of the tumor but of the gonads, may perform the miracle that seems-

Dr ALLEN I think that it is reasonable to consider the case in that light. I hesitate only because tuberculosis involving the small intestine is extremely rare. It usually occurs in the cecum. The cecum may have been involved, but we have no evidence that it was. I think that Dr Robbins would have been able to help more if it had been. Certainly, after the distention had been relieved, a mass should have been palpable in the right lower quadrant. I suppose it is possible for regional ileitis to be present for twenty-five years with extremely few symptoms. I have never seen such a case. The patients I have seen have always had a shorter history or an earlier onset.

Dr. BAUER The patient was so far removed from the onset of the acute attack that she may not have remembered the details.

The character of the stools described made me wonder if we should consider an infectious disease of the small intestine. The stool was white. The patient was never jaundiced and never had dark urine. I should hold out for chronic steatorrhea due to an extensive lesion of the small intestine, such as regional ileitis or tuberculosis.

Dr ROBBINS There was good barium filling of the entire small bowel, and I think that more would have shown in the films if the trouble had been a deficiency state or chronic steatorrhea. The area of narrowing was quite small, which is against regional ileitis. As for the hyperplastic form of tuberculosis, we could not exclude it, but the location is unusual. This was definitely in the ileum, far from the cecum.

Dr. BAUER My only point is that we often get into difficulty and make diagnostic mistakes because we throw away a history and start at a more recent point—in this case five months before admission. A history that goes back twenty-five years is not unlike that in the present case, except for a difference in severity, and I wonder if, because we can find no explanation, we have the right to say that the patient was neurotic.

Dr. NORMAN WILSON I do not believe that we can ignore the history in this case, furthermore, the patient was not neurotic. We carefully considered that possibility. She was an intelligent woman, and the history was a definite one of

trouble that went back twenty-five years but with exaggeration of symptoms for five months before admission. I think that we can accept the history as being all right. The episodes were definite, and between them she was relatively free from symptoms.

Dr ALLEN That bears out Dr Bauer's important criticism of my deduction.

CLINICAL DIAGNOSIS

Small-bowel obstruction, due to long-standing regional ileitis

Dr ALLEN'S DIAGNOSIS

Small-bowel obstruction, due to tumor of terminal ileum, probably malignant

ANATOMICAL DIAGNOSIS

Multiple carcinoids of ileum, with metastases to mesenteric lymph node

PATHOLOGICAL DISCUSSION

Dr TRACY B MALLORY At operation a constricting lesion was found in the small bowel near the terminal ileum. In the mesentery, immediately adjacent to this, was a large, firm metastasis. A short distance away from the first lesion was a second tumor of the ileum. The cut surfaces of the tumors showed small yellow speckles. The larger tumor produced a constriction of the bowel with dilatation of the proximal portion to three times the normal diameter. Despite the dilatation, the wall above the constriction was markedly thickened, so that it is evident that there had been obstruction for a long time. The tumor was composed of extremely small cells containing argentaffin granules, a so-called "carcinoid" of the small bowel. These tumors usually grow extremely slowly. They are invasive and metastasize to regional lymph nodes but do not usually extend beyond them. There is a case in the hospital records in which the bowel was resected, and metastasis to the mesenteric nodes was noted at the time of operation. When the patient died in this hospital sixteen years later of pneumonia, the metastatic carcinoid was found in the mesentery, but it had not spread a centimeter from the original location in all that time.

three hours at a time and occurring two or three times a year for a period of twenty-five years. I think that that type of history might be elicited from a great many schoolteachers of similar age. Perhaps it is unfair to make that classification, but schoolteachers probably have many things to worry about that other people avoid. For five months there had been a definite change in the pattern.

For some reason or other the patient had retired. The age is fairly young for a schoolteacher to stop working, but perhaps it was for reasons other than health, although it is possible that she became more uncomfortable and had to stop working. At any rate, for five months, there were symptoms that may provide a starting point as a present history.

The emphasis on the fact that fatty foods caused dyspepsia, as stated in the record, is interesting but may not have too much bearing on this case, although one must consider the possibility of a gallstone ileus with small-bowel obstruction. The history is not consistent with a gallstone ileus, in that for three or four weeks there should have been fairly acute symptoms simulating acute cholecystitis and preceding the onset of small-bowel obstruction while the fistula was being formed naturally through which the stone would eventually pass into the intestinal tract to become lodged in the terminal ileum at its narrowest point. These patients usually appear in the hospital about forty-eight hours after the onset of obstruction, and as a rule the small bowel is tremendously distended with gas.

Another cause of small-bowel obstruction that must be considered is a foreign body of some type. There are many causes. People swallow enormous boluses of food. A complete orange in two parts may join itself together in the terminal ileum, as we have seen, and cause obstruction. In certain regions of the country there are various forms of bezoar, particularly in the South, where persimmons are eaten, apparently, the fibers get together and cause a bolus that in turn causes intestinal obstruction. Any foreign body, such as a toothpick, may penetrate one wall of the intestine and go into the other and produce the same result.

The most frequent cause of intestinal obstruction in the small bowel is an adhesive band, which often occurs without previous surgery. The patients are liable to be sicker than this patient was, with a high white-cell count, indicating the possibility of gangrene in the bowel and so forth. Usually, there is not a four-day history of acute symptoms prior to entry. I think that we can rule out adhesive bands. Possibly, we cannot rule out torsion of the bowel, which does occur, although not so often in the small intestine as in the large bowel.

The possibility of a Meckel's diverticulum must always be considered in the discussion of intestinal obstruction. This woman gave no indication that she had such a lesion. Although the preoperative

diagnosis is apt to be intestinal obstruction associated with an inflammatory diverticulum, in adults we have the same inflammatory reactions that we have in acute appendicitis, with a high leukocyte count, a mass and a much sicker patient than this woman appeared to be. Intussusception can practically be ruled out on the basis that there was no blood and that the patient is said to have passed two water discharges from the rectum. The fact is stressed that no blood was found.

The nonspecific granulomas, regional ileitis and so forth develop in a slow fashion. They rarely precede an acute situation such as this, unless there is perforation with abscess formation, and there is no indication of that. I believe that Crohn's disease, or terminal ileitis, must be considered in the differential diagnosis, but it is not probable. Two factors in the family history were stressed: a history of cancer in the mother, a maternal aunt and sister, and a death from tuberculosis in a brother or sister. The possibility of a malignant tumor of the small intestine is reasonable, although it is a rare condition — the incidence is so limited that one hesitates to make such a diagnosis. One should be extremely cautious in coming to that conclusion although I must admit that on thinking this case over before I had about decided that I was going to make such a diagnosis. Benign tumors of the intestine are far more frequent. They are, however, usually associated with intussusception. I am not able to read Dr. Robbins's thoughts or to grasp the lead that he tried to give me about the mass underneath this arch of bowel that he has described, and I must say that his efforts do not help me too much.

Having gone through all the various possibilities, I fall back on that of a tumor of the small intestine that had been troublesome for four or five months and that had finally, four days prior to admission, produced an acute obstruction, and I shall therefore make a diagnosis of tumor of the ileum. Incidentally, the farther down the small bowel, the likelier the tumor is to be sarcomatous, the higher up, the likelier it is to be cancer. I do not believe that I want to make a differential diagnosis between adenocarcinoma and sarcoma — or lymphoma, for that matter, there is no evidence of bleeding, however, which is against a carcinoma and in favor of the other type.

DR. WALTER BAUER: I wonder if Dr. Allen is justified in throwing out the history of twenty-five years' duration. I also wonder if one should not entertain the possibility that steatorrhea produced large granulomatous lesions, or one of the infectious granulomas that Dr. Allen has mentioned, such as tuberculosis or regional ileitis. I do not see why that should not fit the whole picture, without the necessity of considering a neoplasm. It would explain all the symptoms and also enable one to account for the difference or increase in symptomatology during the last five months.

thiazole and sulfapyridine, although it may appreciably increase the solubility of sulfadiazine and its derivatives. It also tends to increase the excretion of the latter in the urine, thus partly defeating its purpose. Moreover, the forcing of fluids and the use of alkalis are contraindicated in patients with cardiac or renal insufficiency and also in those with impaired liver function.

These considerations have led to attempts to utilize mixtures of different sulfonamides¹⁻⁵. The rationale for the use of sulfonamide mixtures is based on solubility experiments with combinations of the various effective sulfanilamide derivatives, they showed that if two or more of these compounds are present simultaneously in water or urine, each retains its own solubility, uninfluenced by the presence of the other. In other words, a saturated aqueous or urinary solution of sulfathiazole can still be fully saturated with sulfadiazine and sulfamerazine.²

Lehr¹ used sulfathiazole and sulfadiazine in equal amounts and showed experimentally that this combination produces a low renal toxicity and has a high antibacterial activity. Clinical studies in patients with acute bacterial infection in both adults² and children³ indicated that this mixture given in the total doses ordinarily employed with single compounds yielded uniformly satisfactory therapeutic results. Effective blood levels and high sulfonamide concentrations in the urine were readily maintained with these doses. When treatment was stopped, the mixtures were rapidly cleared from the body. Crystalluria was infrequent despite the intentional omission of adjuvant alkali therapy, and no signs of renal irritation were encountered. The incidence of allergic reactions, moreover, also appeared to be lowered. Similarly, Flippin and his associates⁴ used a mixture containing equal parts of sulfadiazine and sulfamerazine, and they noted that the use of this combination resulted in a markedly decreased incidence of crystalluria compared with that observed when either compound was administered singly.

Extensive studies with sulfonamide mixtures ("sulfa-combinations") have also been carried out by Frisk and his co-workers^{5, 6} in Stockholm. They found that the antibacterial effect of such a com-

bination was equal to the sum of those of the individual components. Their studies showed that when sulfathiazole, sulfadiazine and sulfamerazine were used together each retained its own solubility in buffered solutions or in urine over the usual pH range. The same was true of the acetyl derivatives of these compounds. Experiments in rabbits with these compounds given individually and in combination showed that fewer concretions resulted from the mixture than from any of the individual compounds used separately in equal doses. In human beings the three sulfonamides given simultaneously were found to be absorbed, excreted and acetylated independently.

The most suitable composition per gram was found experimentally to be 0.37 gm of sulfathiazole, 0.37 gm of sulfadiazine and 0.26 gm of sulfamerazine. This mixture had almost the same absorption and excretion relations as sulfadiazine. There was practically no risk from accumulation in the blood, even when high doses were administered. In the doses ordinarily used in the treatment of pneumonia, the combined preparation is not excreted in supersaturated solutions if the reaction of the urine is approximately neutral. With the individual components given in equal doses, on the other hand, either the free or acetylated form always occurs in the urine in supersaturated solution, even in a neutral urine. The Swedish workers thought that the use of this mixture appeared to eliminate the risk of the formation of concretions in normal kidneys. As added precautionary measures, however, they state that diuresis should be maintained and that alkalis should be given. This method is considered to have the advantage of permitting the use of larger doses than usual with less danger of renal complications in cases of infection due to the more resistant bacteria.

So far as the development of sensitization is concerned, a combination of the related compounds sulfadiazine and sulfamerazine appears to be preferable to a combination of sulfathiazole and sulfadiazine. In the former, the two compounds differ only by a single methyl group, sulfamerazine being the monomethyl derivative of sulfadiazine. When used alone, if sensitization to one of these compounds develops it is almost invariably accom-

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

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MATERIAL should be received not later than noon on Thursday, three weeks before date of publication

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A M A CENTENNIAL

ONE hundred years ago the American Medical Association had its inception, and although little of great import was accomplished during the first fifty years of its existence, it has made many significant contributions to the advance of medicine during the past fifty years. Among others, these include improved standards for medical schools and hospitals, investigation of quacks and charlatans, approval of drugs, foods and apparatus, professional and lay education, promotion of industrial and rural health and investigation of matters pertaining to the economic aspects of medical practice. Those who were unfamiliar with these achievements must have been made duly conscious by the series of articles covering the history of the Association that

recently appeared in the *Journal of the American Medical Association*, from the pen of its editor, Dr. Morris Fishbein.

The *Journal* extends heartiest congratulations to the Association on the occasion of its hundredth anniversary. No doubt the celebration in Atlantic City will be an event whose memory those who attend will cherish for many years to come.

PREVENTION OF RENAL COMPLICATIONS BY THE USE OF SULFONAMIDE MIXTURES

PENICILLIN, because of its high therapeutic efficacy coupled with its low toxicity, has probably displaced the sulfonamide drugs in the treatment of many types of infection. Streptomycin, likewise, has proved highly effective in a number of other types of infection, for some of which the sulfonamides had previously been used with varying degrees of success. There are still numerous infections, however, for which the sulfonamide drugs continue to be useful and even essential, either alone or as an adjunct to other therapy, and this will probably remain true for some time to come.

Among the most frequent of the serious complications attending the use of the more effective sulfonamide compounds are those involving the urinary tract. These are caused predominantly by mechanical factors associated with the precipitation of crystals of the free or acetylated drugs anywhere along the urinary tract, and they are most serious when the precipitation occurs within the kidney tubules. These complications are dependent, in turn, largely on the solubility and the concentration of the compounds in the urine. Any measures that increase their solubility or prevent their excessive concentrations in the urine should therefore diminish the frequency with which precipitation occurs and hence reduce the incidence of renal complications.

The methods generally employed for this purpose are the forcing of fluids, with a view to producing a more dilute solution, and alkalization of the urine, for the purpose of increasing the solubility of the drugs as they are excreted. These methods have not always brought about the desired effects. Furthermore, alkalization does not markedly affect the solubility of some compounds, notably sulfa-

manently injured, and even distorted, in the school room, in consequence of the neglect of the proper authorities to furnish chairs. Thanks to an enlightened age and the progress of common sense in our city, seats have been introduced at last, properly constructed — An impulse is likely to be given to a much neglected subject, by the energy of the Mass Agricultural Society. On Friday evening, April 16th, a lecture was given in the hall of the House of Representatives, in this city, by Dr Warren, on the general anatomy of the horse. We cheerfully accord to him the honor of having opened a sealed volume in Massachusetts, and thank him, too, in the name of humanity, for this kind effort to lessen the sufferings of this noble and useful animal — On Wednesday last, according to previous arrangements, the National Medical Convention assembled in Philadelphia at an early hour, and organized for the despatch of business. The manner in which the delegates were received by the medical profession of Philadelphia was exceedingly cordial and gratifying. The Convention held its daily sessions in the elegant hall belonging to the Academy of Natural Sciences, located on Broad street. A series of hospitalities characterized the intercourse of the representatives with the medical gentlemen of Philadelphia, which will not soon be forgotten by the former. Dr Stewart, of New York, offered the following resolution on the final day: "Resolved, That all unfinished business be referred to the American Medical Association about to be organized. Resolved, That the Convention do now resolve itself into the 'American Medical Association' and that the officers of the Convention continue to act as officers of the Association until others are appointed." Agreed to — Extracted from the *Boston Medical and Surgical Journal*, April and May, 1847.

R F

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

BLACK — James S. Black, M.D., of Nashua, died April 21. He was in his seventy-third year. Dr. Black received his degree from Dartmouth Medical School in 1901. He was a fellow of the American College of Surgeons. His widow and a daughter survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

NEW APPOINTMENTS

Robert E. S. Kelley, M.D., a retired captain of the Regular Medical Corps of the United States Navy, has been appointed to the Division of Biologic Laboratories as physician in charge of the second mobile unit of the State Blood Donor Pro-

gram. During more than twenty-nine years in the Navy, Dr. Kelley served as public-health officer of Guam and was loaned to the Republic of Haiti for public-health work for over two years.

Walter J. Pennell, M.D., who retired from the Navy with the rank of captain after nearly thirty years' service in the Medical Corps, has been appointed health officer of the Northeastern District of the Massachusetts Department of Public Health. During his Navy career, Dr. Pennell served as medical officer in command of naval hospitals at Trinidad, British West Indies, Parris Island, South Carolina, and Newport, Rhode Island. He also served as executive officer and consultant in internal medicine and lecturer in cardiology, Navy Medical School. He is a diplomate of the American Board of Internal Medicine.

Paul Richmond, M.D., formerly a captain in the Medical Corps of the United States Navy, has been appointed health officer of the Worcester district of the Massachusetts Department of Public Health. A medical officer in the Navy since 1915, Dr. Richmond served overseas in New Guinea, Australia and the Philippine Islands.

Mary Carr Baker, A.B., has been appointed personnel training co-ordinator of the Massachusetts Department of Public Health. Mrs. Baker will direct in-service training programs and co-ordinate the teaching programs of professional schools, organizations and other agencies participating in public-health teaching. Mrs. Baker was formerly field-program supervisor of the Massachusetts Blood Donor Program.

Robert G. Benson has been appointed field-program supervisor of the Blood Donor Service of the Massachusetts Department of Public Health. Mr. Benson will represent the Department in collaborative activities with the American Red Cross and community organizations and in arranging for local participation in the blood donor program. Mr. Benson has wide field experience, having served for sixteen years as a food and drug inspector with the Massachusetts Department of Public Health.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

CLINIC	DATE	CLINIC CONSULTANT
Salem	June 2	Paul W. Hugenberger
Haverhill	June 4	William T. Green
Gardner (Worcester subclinic)	June 4	John W. O'Meara
Lowell	June 6	Albert H. Brewster
Greenfield	June 9	Charles L. Sturdevant
Springfield	June 17	Garry deN. Hough, Jr.
Pittsfield	June 18	Frank A. Slowick
Brockton	June 19	George W. Van Gorder
Worcester	June 20	John W. O'Meara
Fall River	June 23	David S. Grice
Hyannis	June 26	Paul L. Norton

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments.

panied by sensitization to the other, hence, there is no added disadvantage from using both at the same time, and if the patient becomes sensitized, sulfathiazole can be safely used in 85 per cent of the cases. The combination of sulfathiazole and sulfadiazine, on the other hand, would probably result in sensitization to both, and no one of the three drugs could then be given without a reaction.

REFERENCES

- 1 Lehr, D. Inhibition of drug precipitation in urinary tract by use of sulfonamide mixtures: sulfathiazole-sulfadiazine mixture. *Proc Soc Exper Biol & Med* 58:11-14, 1945.
- 2 *Idem*. Prevention of renal complications by therapeutic employment of sulfonamide mixtures: sulfathiazole-sulfadiazine combination. *J Urol* 55:548-566, 1946.
- 3 Lehr, D., Slobody, L., and Greenberg, W. Use of sulfadiazine-sulfathiazole mixture in treatment of children. *J Pediatr* 29:275-285, 1946.
- 4 Flippin, H. F., and Reinhold, J. G. Evaluation of sulfonamide mixtures and various adjuvants for control of sulfonamide crystalluria. *Ann Int Med* 25:433-442, 1946.
- 5 Frisk, A. R., Hagerman, G., Helander, S., and Sjögren, B. Sulfakombination — En ny kemoterapeutisk behandlingsprincip. *Nord med* 29:639-651, 1946.
- 6 *Idem*. "Sulpha-combination" — new chemotherapeutic principle. *Brit M J* 1:7-10, 1947.

A HUNDRED YEARS AGO

The trustees of the Massachusetts General Hospital and the McLean Asylum present for the last year an exceedingly favorable report of these institutions. In both the income has exceeded the expenditures, leaving a balance to be appropriated for increased comforts and advantages. One who visits the Allen St. Hospital cannot fail to be struck with the neatness with which wards have been finished and the conveniences with which they are furnished. — The practitioner of medicine has a stomach to be filled, a body to be clothed, and in most cases a family to maintain. To do so, there must be an adequate income from some source to meet the expense of being a part and parcel of the general population. But very few medical practitioners, in this country, begin life with property, those who have that advantage rarely trouble themselves about the details of practice — unless it is for the purpose of maintaining a family position. Physicians are not as successful in the gathering up of property as gentlemen of the law, merchants, or active, bold, operating mechanics. The fees of lawyers are regulated either by special law, bar rules, or custom, in a manner that secures to them every fraction of their dues. Merchants and mechanics most generally, in their bargains, both require and give security, without giving offense, but the physician goes wherever called, not knowing whether he is to be paid or not. His losses, therefore, are immense in the course of a life of medium length. His capital is earning nothing unless he renders a personal service. Every physician is satisfied that one half of his practice, at least, is utterly lost, and per-

haps more. The vulgar impression that the practice of medicine is a profitable business is not true with the mass of the profession, the number of physicians who have made themselves rich in legitimate practice is so small, as hardly to be recognized either in town or country. — Valuable as the Boston Lying-in Hospital proves to be, its locality is exceedingly objectionable, and some effort should be made to bring it down into the heart of the city, where it should have been placed at first. The land might be sold to good advantage, and the money expended equally advantageously in the purchase of a large, convenient house nearer to the center of population. As the patients are not on charity, but pay a small fee, probably the number would be quadrupled were the establishment down in town. It would also better accommodate the directors, the physicians, and every person, in fact, who has any connection with it. — We learn that the Corporation of Harvard University, since the resignation of Dr. Warren, have appointed three new professors, two of whom are to be attached to the Massachusetts Medical College in Boston, and one to the University at Cambridge. The new incumbents are, Oliver W. Holmes, M.D., Professor of Anatomy and Physiology (this is called the Parkman Professorship of Anatomy and Physiology in honor of Dr. George Parkman, a distinguished benefactor of the Medical School), John B. S. Jackson, M.D., Professor of Pathological Anatomy and Curator, and Jeffries Wyman, M.D., Hersey Professor of Anatomy at Cambridge. All the above gentlemen are well known to the public as working men, who by their own talents and persevering industry, have raised themselves to the head of the department in science which they are respectively to teach. We are gratified that the choice of the Corporation has fallen on candidates in whose favor we believe the general suffrage of the medical profession in Massachusetts would have cordially united. — The Philadelphia Medical Examiner believes it is now ascertained by numerous experiments, that sulphuric ether alone possesses the virtues claimed for the "letheon" or "compound gas." Since it is generally conceded both in this country and Europe, that the patent is invalid so the repugnance felt towards any extended notice of the matter is removed, and the Examiner will from time to time notice the experiments and observations made in various parts of the world, confirmatory or otherwise of the good effects of this extraordinary agent. — Through the unwearied exertions of Joseph W. Ingraham, Esq., an efficient member of the Boston Primary School Committee, chairs have been introduced into our public schools for children. Strange, with the foresight and characteristic wisdom of our Puritan forefathers, that they should have overlooked the comfort of a school seat with a back. Certain it is that backs, bones and limbs have more or less been per-

Here is one of a projected series entitled *Monographs on Progress of Research in Holland*. It should be in every reference medical collection.

Cardan. By James Eckman. 4° paper. 120 pp. Baltimore: Johns Hopkins Press, 1946. \$2.00.

During the Renaissance and for an additional period of over a hundred years the University of Padua numbered among its students and professors such great persons as Thomas Linacre, Vesalius, Copernicus, Georgius Agricola, William Harvey, Galileo, and many others including Cardan. The author has made an analytical study of the life and time of Cardan—physician, mathematician and scientist—based on his works and on the mass of writings of the commentators. Cardan, no unfavorable testimony has been suppressed. Cardan—of three hundred and thirty-five references cited in the book concludes the work. Although the works of Cardan are cited throughout the text, it is to be regretted that a bibliography of his published writings was not included in the dissertation. The great and now scarce *Opera*, published in ten volumes at Lyon in 1663, should be in all large medical history collections. Likewise, this analytical dissertation by Eckman should be in all medical-history collections.

History of agency of health service. By Malcolm W. Carr. D.S. Studies of the New York Academy of Medicine. Committee on Medicine and the Changing Order. 8°, cloth. 1 pp. New York: The Commonwealth Fund, 1946. \$1.50. This monograph presents a comprehensive picture of dentistry in the United States including its history and development, present activities and problems and some indications of future trends. The work is divided into six parts: history, education, practice, research, socioeconomic aspects, a summary and conclusions. A short preliminary chapter devoted to the present status of organized dentistry. The part on history covers the period from ancient Egypt to the present time with emphasis on American accomplishments. Education is discussed under the topics of pre-dental education, curriculum, graduate education and hospital relationships and residencies. Dental practice is divided into three in general, including the hygienist, the assistant and laboratory technician, licensure and control and specialization, hospital service, dentistry in industry, public-health dentistry, dentistry in rural areas, dentistry for Negroes, denture dentistry, and national dental legislation. The section on public-health dentistry, which discusses dentistry in public schools, is too short and sketchy and could have been filled with benefit to all persons interested in this phase of the health service. The material is logically arranged but the treatment is uneven and somewhat sketchy in parts. Likewise, the list of references appended to the topics are uneven in distribution giving the impression that portions of the literature have been inadequately covered. The monograph should prove useful to all interested persons, however, and should be in all libraries as a reference source.

Testing Techniques of manual examination. By W. Daniels, M.A., Marian Williams, M.A., and Catherine Whittingham, M.A. 4°, paper, 189 pp. Designed and illustrated by Harold Black with 349 diagrammatic line drawings. Philadelphia and London: W. B. Saunders Company, 1946. \$2.50.

Students, physical therapists and physicians interested in manual medicine, orthopedics and neurology will find this a useful reference and valuable teaching aid. Noteworthy features are the numerous and excellent drawings of the organization of the material. In addition to clear explanations of the technique of manual strength tests of all the muscles there is assembled on the same page the normal range of joint motion, the origin and insertion of the muscles, with anatomical diagrams and the innervation of peripheral nerves and spinal-cord segments.

Complete Handbook on State Medicine. By J. Weston Welch. Paper, 170 pp. Portland, Maine: J. Weston Welch, 1946.

The national high-school debating topic for the school 1946-1947 is state medicine defined as medicine sup-

ported by federal, state or local government. This handbook is primarily designed for high-school debaters and covers both sides of the question. The general and medical literature on the subject has been examined and three hundred and forty-seven quotations for the affirmative and three hundred and forty-four for the negative comprise a large part of the text. The preliminary chapters discuss the question in general including the history of medical plans in the United States and abroad. Although the author believes that a bill similar to the Murray-Wagner-Dingell Bill will not be passed by the next Congress, such matters will prove to be of great concern to the medical profession when the next economic depression occurs unless voluntary medical plans become prevalent before that time. Mr. Welch is well known in educational circles having written debate handbooks on the national and college debate questions since 1926. The material is well organized for its purpose and should prove of value to all medical libraries and physicians and other persons interested in the subject since it provides six hundred and ninety-one direct references to the topic.

Injury and Death under Workmen's Compensation Laws. By Samuel B. Horowitz. 1 B. LI. B. Second printing. 8°, cloth. 486 pp. Boston: Wright and Potter Printing Company, 1946. \$6.00.

The first printing in September 1944 of this authoritative treatise on workmen's compensation was exhausted early necessitating this second printing. The work is divided into four parts. The first, third and fourth deal with the historical and legal aspects of the subject. The second part—on personal injury by accident arising out of and in the course of employment—should prove valuable to all physicians and surgeons who come into contact with cases of injury and compensable diseases. This book should be in all medical libraries and in the libraries of surgeon and physicians interested in the subject.

BOOKS RECEIVED

The receipt of the following books is acknowledged and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Demonstrations of Physical Signs in Clinical Surgery. By Hamilton Bailey, F.R.C.S. (Eng.) F.I.C.S. Surgeon, Royal Northern Hospital, London; surgeon and urologist, County Hospital, Chatham; and senior surgeon, St. Vincent's Clinic and Italian Hospital. Tenth edition, revised. 8°, cloth. 375 pp. with 573 illustrations. Baltimore: Williams and Wilkins Company, 1946. \$7.00. Printed in Great Britain.

This excellent manual first published in 1927 has enjoyed a great popularity. Ten editions and seven reprints have so far been necessary. The book has been translated into Spanish and Portuguese and Italian and Greek translations are in active preparation. The manual has been thoroughly revised and is intended for the use of students and interns. The material is well arranged, and the text well printed with a good readable type on good paper. The illustrations are excellent. An adequate index concludes the volume. The price seems excessive.

Health Instructor Yearbook, 1946. Compiled by Oliver E. Byrd, Ed.D., associate professor of hygiene, Stanford University. 8°, cloth. 599 pp. Stanford University: Stanford University Press, 1946. \$5.00.

This volume is the fourth of a series first published in 1943. It comprises abstracts of three hundred and eighty-four articles appearing in the current literature. The compiler in assembling the abstracts read fifteen hundred and twelve articles in various scientific, medical, statistical and public-health journals. The material covers the whole field of public health in its various aspects and a new chapter on international health has been added to this issue. The abstracts are numbered, and a complete list of references as well as author and subject indexes is appended to the text. The abstracting is well done, and the book well printed.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR APRIL, 1947

RÉSUMÉ

DISEASES	APRIL 1947	APRIL 1946	SEVEN YEAR MEDIAN
Chancroid	3	2	2*
Chicken pox	2657	1751	1286
Diphtheria	46	15	14
Dog bite	1064	1216	1073
Dysentery, bacillary	7	10	2
German measles	102	1191	523
Gonorrhea	332	453	368
Granuloma inguinale	1	0	0*
Lymphogranuloma venereum	2	1	4*
Malaria	3	35	3
Measles	1756	8612	4012
Meningitis, meningococcal	9	14	16
Meningitis, Pfeiffer-bacillus	5	3	2
Meningitis, pneumococcal	3	7	7†
Meningitis, staphylococcal	0	0	0†
Meningitis, streptococcal	0	0	2†
Meningitis, other forms	1	0	0†
Meningitis, undetermined	2	4	5†
Mumps	1131	924	1483
Pneumonia, lobar	203	128	350
Poliomyelitis	0	2	1
Salmonellosis	16	3	5
Scarlet fever	488	824	1422
Syphilis	303	454	454
Tuberculosis, pulmonary	288	225	225
Tuberculosis, other forms	18	12	17
Typhoid fever	3	2	2
Undulant fever	5	9	4
Whooping cough	499	476	604

*Three-year median

†Five-year median

COMMENT

The upward trend in the number of cases of diphtheria since July of last year has finally halted. The number of cases reported in April is approximately half the record for March, however, the number of cases is still approximately three times as great as in April, 1946 and three times the seven-year median. This drop was partly due to the usual seasonal decline, but undoubtedly the active immunization programs that have been conducted throughout the Commonwealth during the past few months are having an effect.

The drop in the number of cases of measles and German measles noted last month was more marked in April, both diseases being much below the seven-year median for the month.

Scarlet fever showed a marked drop, there being half the number of cases reported for April, 1946, and one third the seven-year median.

Diseases above the seven-year median for the month are chicken pox, bacillary dysentery, typhoid fever and undulant fever.

Below the seven-year median are dog bite, mumps, lobar pneumonia, poliomyelitis and whooping cough.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Actinomycosis was reported from Springfield, 1, total, 1. Diphtheria was reported from Arlington, 1, Boston, 17, Brookline, 1, Cambridge, 9, Canton, 1, Chelsea, 1, Everett, 1, Framingham, 1, Hinsdale, 1, Lowell, 2, Lynn, 2, Malden, 2, Medford, 2, Rockland, 1, Saugus, 1, Stoneham, 1, Wakefield, 1, Worcester, 1, total, 46.

Dysentery, amebic, was reported from Fitchburg, 1, New Bedford, 1, total, 2.

Dysentery, bacillary, was reported from Boston, 1, Melrose, 1, Worcester, 5, total, 7.

Malaria was reported from Boston, 1, Medford, 1, Raynham, 1, total, 3.

Meningitis, meningococcal, was reported from Boston, 3, Cambridge, 1, Fall River, 1, Holbrook, 1, Lenox, 1, Somerville, 1, Wakefield, 1, total, 9.

Meningitis, Pfeiffer-bacillus, was reported from Framingham, 1, Lynnfield, 1, Seekonk, 1, Worcester, 2, total, 5.

Meningitis, pneumococcal, was reported from Ashland, 1, Haverhill, 1, Springfield, 1, total, 3.

Meningitis, other forms, was reported from Boston, 1, total, 1.

Meningitis, undetermined, was reported from Cambridge, 2, total, 2.

Salmonellosis was reported from Boston, 3, Chicopee, 1, Holyoke, 1, Ludlow, 1, Lynn, 1, Palmer, 1, Salem, 1, West Bridgewater, 3, Worcester, 4, total, 16.

Septic sore throat was reported from Amesbury, Boston, 10, Everett, 1, Grafton, 2, Haverhill, 1, Medford, Merrimac, 2, total, 18.

Trichinosis was reported from Attleboro, 2, Boston, total, 6.

Typhoid fever was reported from Beverly, 1, Boston, Watertown, 1, total, 3.

Undulant fever was reported from Auburn, 1, Lancaster, Worcester, 3, total, 5.

BOOK REVIEWS

Neurosis and the Mental Health Services By C P Blacke, M.A., M.D., F.R.C.P. With a foreword by Sir Wilko Jameson, K.C.B., M.A., M.D., LL.D., F.R.C.P. 8°, cloth 218 pp., with 56 tables. New York: Oxford University Press, 1946. \$5.00.

This book is a review of present-day thinking and planning for psychiatry in England. It is a report of a serious and systematic survey of current problems and trends worked out in the careful and methodical way for which civil commissions in the British Isles are famous. It contains a great mass of detailed information and much discussion of nearly every phase of mental health so far as it is the responsibility of mental health services and also certain essential points and conclusions that are worth noting.

In the first place, between 1938 and 1942, there was an increase in the numbers and proportions of neurotic patients seen at two hundred and sixteen psychiatric clinics in England and Wales. The investigators who undertook this study came to the conclusion that this phenomenon did not represent a real increase of neurosis attributable to the war but rather a growing use of the country's psychiatric services by general practitioners, they believed that it might have occurred in the absence of war. Secondly, cases of neurosis attributed by psychiatrists to the effects of air raids were astonishingly few. And, finally, one of the most significant facts revealed is the marked disparity in the psychiatric services available in different parts of the country. The best facilities were found in London and the poorest in Wales.

The original purpose of this survey was to throw light on how the outpatient psychiatric services had been affected by the war. It was carried out by thirty-three investigators, who carefully combed the eleven civil defense regions of England and Wales for facts. In doing this they concerned themselves primarily with outpatient services. Psychiatric wards and child-guidance services were not included. Thus, the report deals with ambulatory cases of psychoneurosis for the most part, and relatively little emphasis is given cases requiring inpatient facilities and institutional care, which are dealt with regularly in the annual reports of the mental hospitals, whereas this report is the first of its kind published since the war and one of the few ever published.

The book is a valuable source of well documented facts and unique as an up-to-date volume for reference.

Modern Development of Chemotherapy By E. Havinga, H. W. Julius, H. Veldstra and K. C. Winkler. 8°, paper, 175 pp., with 31 illustrations and 8 tables. New York: Elsevier Publishing Company, Incorporated, 1946. \$3.50.

Research in Holland continued intensively in all directions during World War II, and this monograph reviews the work done in the field of chemotherapy during the war period ending on V E Day. The review is necessarily confined to material published in Dutch periodicals, since reports from other countries were not available. The work is confined to the sulfonamides and is divided into the following sections: mechanism of the action of the sulfonamides and of para-aminobenzoic acid, chemical investigations devoted to the synthesis and activity of sulfanilamide derivatives and related compounds, and pharmacologic, immunologic and clinical investigations. The last chapter, by J. J. Duyvené de Wit, discusses a new drug "Expansine." In the section on chemistry is given a tabular list of seventy-three synthetic compounds with their chemical structure and activity. To each special section is appended a list of references of the work of Dutch authors published at home and abroad. The material is well organized and well published in every way. The

Pharmacology and Therapeutics Originally written by Arthur Cushman, M.A., M.D., LL.D., F.R.S. By Arthur Grollman, Ph.D., M.D., professor of medicine and chairman, Department of Experimental Medicine, and professor of pharmacology and chairman, Department of Physiology and Pharmacology, Southwestern Medical College, attending physician, Parkland Hospital, and consultant in internal medicine, Baylor University Hospital, and Donald Slaughter, M.D., dean of University of South Dakota School of Medical Sciences. Thirteenth edition, thoroughly revised 8° cloth, 744 pp., with 74 illustrations Philadelphia Lea and Febiger, 1947 \$3.50

This standard reference book, first published in 1899, has been thoroughly revised and brought up to date by the new material in the fields of chemotherapy, endocrinology and the vitamins has been incorporated, and some of the older out-of-date material has been deleted. The present edition is in accord with the *USP XII* and the *Pharmacopoeia*, 1932. A list of selected references is appended to each chapter. A comprehensive index concludes the volume. The book is well published and is recommended for all medical libraries and allied libraries, it should be useful as a reference book for the physician and the medical student.

Endocrinology By Robert B. Greenblatt, M.D., C.M., professor of endocrinology, University of Georgia School of Medicine and director, Sex Endocrine Clinic, University Hospital, Augusta, Georgia. With a foreword by G. Lomax Kelly, M.D., dean, University of Georgia School of Medicine. Third edition 8°, cloth, 302 pp., with 58 figures, color plates and 20 tables and charts. Springfield, Illinois Charles C. Thomas, 1947 \$4.75

This edition of a standard book has been enlarged and brought up to date. It is intended for the busy, general practitioner and is written accordingly with emphasis on treatment. The material is well organized and considered under female and male endocrinology and hormonology. The chapters are short and concise, and a short list of pertinent references is appended to each. The volume is well published in the usual Thomas style. The various separate sets of numbers of figures and tables for each chapter are confusing and not good for reference purposes. (Consecutive numbering throughout the volume is more satisfactory for general use.) The usefulness of the work is attested by its popularity, requiring three editions and one extra printing since its first publication in 1941.

The Story of Human Birth By Alan Frank Guttmacher, M.D., associate professor of obstetrics, Johns Hopkins University School of Medicine, visiting obstetrician, Johns Hopkins Hospital, and chief in obstetrics, Sinai Hospital, Baltimore. Paper, 214 pp., with 7 illustrations. New York: Pennington Books, Incorporated, 1947 25 cents

Originally published in 1937 by the Viking Press under the title *Into This Universe*, the text has been cut and condensed from the original but has been revised and brought up to date for this popular pocket edition. The presentation is revised, the material well organized, and the text written in plain language for the laity. Appended to the text is a list of books for recommended reading. This list may have been suitable for the original edition of 1937 but seems out of place in this inexpensive issue. It is incongruous to suggest the reading of Paré, Mauriceau, Guillemeau, Roesslin and Raynalde in the early rare English editions, obtainable in large medical libraries. Also, the technical references to the placenta, the embryo, various aspects of labor and the puerperium, even in the German language, are out of place in this type of book.

In late years there has been a decided improvement in the standard of medical books written for the general public and more physicians of high professional standing are writing such books, providing a decided contrast to the low standard of popular output of the past decade.

Physiological Chemistry By Philip B. Hawk, Ph.D., Food Research Laboratories, Incorporated, and L. Oser, Ph.D., director, Food Research Laboratories

Incorporated, and William H. Summerson, Ph.D., associate professor of biochemistry, Cornell University Medical College. Twelfth edition 8°, cloth, 1323 pp., with 329 illustrations. Philadelphia: Blakiston Company, 1947 \$10.00

This standard textbook which was first published in 1907 has enjoyed a continuous existence of forty years, and for this twelfth edition the subject matter has been completely brought up to date in the light of present-day knowledge. Many chapters have been entirely rewritten, and much new material added, including sections on the polarograph, isotopes, sulfonamides, metabolic antagonists and antibiotics, vitamins, Warburg tissue-slice procedure, photometric analysis, electrophoretic fractionation of plasma proteins and composition of foods. Many new quantitative procedures for blood and urine analysis have been added. Obsolete and minor material has been deleted. The text is well arranged and well documented with tables and formulas. A short pertinent bibliography is appended to each chapter. A comprehensive index concludes the volume. The book is well published in every way and the publishers are to be congratulated on the use of a light-weight but substantial paper for such a large volume. The book is recommended for all medical libraries and for the libraries of all physicians and others interested in the subject.

The Lung By William Snow Miller, M.D., Sc.D. Second edition 8°, cloth, 222 pp., with 168 illustrations. Springfield, Illinois: Charles C. Thomas, 1947 \$7.50

In this second edition of his authoritative monograph on the structure of the lung Dr. Miller has not made any fundamental changes in the text. Some additional illustrations have been added. The results of Professor O. Larzell's studies on the nerves of the visceral pleura have been incorporated in the chapter on the pleura. During the period between the publication of the first edition in 1937 and the present edition the author has not found any reason for changing his opinion that there is an epithelium lining the alveoli of the lung and that it is continuous although some investigators think differently. A long bibliography is appended to the text. The type, printing and illustrations leave nothing to be desired. The publisher has surpassed his usual high standard of publication. The monograph is recommended for all medical libraries and to all physicians and others interested in the lungs.

Gynecological and Obstetrical Pathology With clinical and endocrine relations By Emil Novak, M.D., Sc.D. (Hon., Dublin), associate in gynecology, Johns Hopkins University School of Medicine, and gynecologist, Bon Secours and St. Agnes hospitals, Baltimore. Second edition 8°, cloth, 570 pp., with 545 illustrations, 15 in color. Philadelphia: W. B. Saunders Company, 1947 \$7.50

This standard work has been revised to include advances since the publication of the first edition in 1938. Over a hundred new illustrations have been added, and the selective bibliographies have been brought up to date. The volume is well published in every way. The art work is excellent. This authoritative text is recommended for all medical libraries.

Science Digest Reader A selection of outstanding articles published in *Science Digest* during the past ten years 8°, cloth, 310 pp. Chicago: Windsor Press, 1947 \$3.00

This collection of articles originally condensed and published in *Science Digest* contains many of medical interest, including those on health, personal and mental hygiene, common diseases, diet, drugs and anesthesia. The general scientific articles on atomic energy, rockets and jet planes, radar, the weather and other topics are informative and interesting. The book is well published and should prove useful as light reading in any medical-history collection.

A Surgeon's Domain By Bertram M. Bernheim, M.D., associate professor of surgery, Johns Hopkins University School of Medicine, and visiting surgeon, Johns Hopkins

with a good large type on soft paper. The whole series of volumes, 1943-1946, is recommended for medical and public libraries and should prove of value to all persons interested in public health.

Hospital Care of the Surgical Patient. A surgeon's handbook With an appendix, "The Treatment of Wounds." By George Crile, Jr., M.D., surgeon, Cleveland Clinic, and Franklin L. Snively, Jr., M.D., assistant surgeon, Cleveland Clinic. With a foreword by Evarts A. Graham, M.D., Bixby Professor of Surgery, Washington University School of Medicine, Saint Louis. Second edition. 8°, cloth, 288 pp., with 25 illustrations. Springfield, Illinois: Charles C. Thomas, 1946. \$3.50.

This manual, which is written primarily for the young surgeon about to begin graduate study of surgery, combines in a small volume the clinical, physiologic and technical principles important in the care of the surgical patient. The work is divided into the following sections: physiologic principles, surgical complications, preparation of the patient for operation, postoperative care, technic of hospital procedures and treatment of wounds. There is an important chapter on the relations of the house officer to the patient and his relatives, and to the hospital and department personnel. This manual should prove useful to the young surgeon.

Textbook of Medical Treatment. By various authors. Edited by D. M. Dunlop, B.A. (Oxon), F.R.C.P. (Edin.), M.R.C.P. (Lond.), professor of therapeutics and clinical medicine, University of Edinburgh, and physician, Royal Infirmary, Edinburgh, and L. S. P. Davison, B.A. (Camb.), M.D., F.R.C.P. (Edin.), F.R.C.P. (Lond.), and J. W. McNee, D.S.O., D.Sc., M.D. (Glas.), F.R.C.P. (Edin.), F.R.C.P. (Lond.). Fourth edition. 8°, cloth, 923 pp. Baltimore: Williams and Wilkins Company, 1946. \$5.00.

This popular treatise written by a number of English authorities, first published in 1939, has been completely revised and brought up to date. The format has been changed by enlargement in the size of the page, resulting in a reduction in the number of pages by about 25 per cent although the amount of text has been slightly increased. A new chapter on penicillin has been added. The sections on venereal diseases and diseases of the thyroid gland have been almost entirely rewritten, and the chapter on diseases of the respiratory system has been extensively revised. A postscript contains a short account of DDT as a means of preventing tropical diseases. A valuable appendix comprises a table of official preparations with their proprietary names. Emphasis has been placed on general management in therapy rather than on a mere enumeration of drugs and other therapeutic agents. A comprehensive index concludes the volume, which is well published in every way. The material is of necessity condensed, but the book should prove valuable as a reference work because of the view it gives of British therapeutics.

Le malattie del sangue manuale per medici e studenti. By Adolfo Ferrata, Clinico Medico della Università di Pavia. 8°, cloth, 751 pp., with 289 illustrations, of which 112 are colored, and 6 colored plates. Milano: Società Editrice Libreria, 1946.

This special treatise is based on an experience of over forty years in the study of hematology by the late Professor Ferrata. The whole subject is covered including the blood and blood-forming organs. The material is well organized, and a simple classification is used. The first chapter is on the morphology, genesis and physiology of the blood, including sections on blood-grouping and the velocity of sedimentation of erythrocytes. This is followed by chapters on the anemias, leukemias, hemorrhagic diatheses, malignant granuloma, mononucleosis, reticulosis, polyglobulism and polycythemia, diseases of the spleen and cytologic alterations of the blood in infectious diseases, with a chapter on the technic of blood research. A good index concludes the volume. The text is well printed with a good type. The color illustrations are excellent. This book reflects the best Italian practice and should be in all large medical libraries and in special collections on the blood.

Hygiene. A textbook for college students on physical and mental health from personal and public aspects. By Florence Meredith, M.D. Fourth edition. 8°, cloth, 838 pp., with 155 illustrations. Philadelphia: Blakiston Company, 1946. \$4.00.

This standard textbook, first published in 1926 and revised in 1941, has been entirely reset and revised to include the advances in knowledge of the past five years. The material has been rearranged with the objective of dividing the subject into its logical major divisions. It is expected that this new arrangement will afford the student the opportunity of seeing the whole field of health as a unit and of evaluating its various separate fields. The material is well arranged and the text is well printed with a good type on good paper. The illustrations are adequate for their purpose. The book is recommended for all educational and public libraries and should be useful as a ready reference source in medical libraries.

Digitalis and Other Cardiotonic Drugs. By Eli Rodin Movit, M.D., internist, Veterans Administration Facility, San Francisco. 8°, cloth, 204 pp., with 12 figures and 9 tables. New York: Oxford University Press, 1946. \$5.75.

In this monograph the author has brought together all the available literature on digitalis and its glycoside derivatives, as well as on strophanthus, squill and cardiotonic agents of plant and animal origin. The two botanical species of digitalis—*folium* and *lanata*—are discussed at length in their physiologic, pharmacologic, toxic and clinical aspects. Digilamid, lanatoside C and digoxin, derivatives of the *lanata* species, are considered at length. A special chapter is devoted to strophanthin, the active principle of strophanthus, another to squill and its derivatives. Thevetin and bufotalin, a toad poison, as well as other glycosides of plant origin, are briefly considered. The author discusses the relative merits of the various substances and their clinical indications. A bibliography is appended to each chapter. The text is well printed with a good type on good paper. The monograph is recommended for all medical libraries and should be of value to physicians interested in heart disease.

The New Science of Surgery. By Frank G. Slaughter, M.D. 8°, cloth, 286 pp. New York: Julian Messner, 1946. \$4.00.

Dr. Slaughter has written an interesting narrative for the layman on the recent advances in surgery. He discusses shock, anesthesia, penicillin and the sulfonamides, operation on the chest, pancreas, brain and heart, vascular surgery, treatment by cold, burns, plastic surgery of the face, psychosomatic surgery and cancer. This volume is recommended for public libraries and as light reading for medical students.

Modern Dermatology and Syphilology. By S. William Becker, M.D., clinical professor of dermatology, University of Chicago School of Medicine, and Maximilian E. Obermayer, M.D., clinical professor and chairman, Department of Dermatology, University of Southern California School of Medicine. Second edition. 4°, cloth, 1017 pp., with 461 illustrations and 37 color plates. Philadelphia: J. B. Lippincott Company, 1947. \$18.00.

This treatise has been revised and brought up to date. The use of Dioxan, penicillin and the sulfonamides is discussed. The chapters on therapy and pigmentary dermatoses have been enlarged. The chapter on trophic and deficiency diseases has been completely rewritten to reflect the advances in vitamin therapy. There are new chapters on leprosy and tropical diseases. In the newly revised section on syphilis the value of quantitative serologic and verification tests for diagnosis, rapid treatment methods and the use of penicillin are discussed. A classification chart has been appended to the chapter on cutaneous diseases due to animal organisms. The text is well printed with a good type in a two-column format, but the weight is much too heavy for the volume to be easily handled. All color plates are tipped in and a lighter paper could have been used to advantage. The book is recommended for all medical libraries.

The New England Journal of Medicine

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Volume 236

JUNE 5, 1947

Number 23

PREGNANCY FOLLOWING LUMBODORSAL SPLANCHNICECTOMY FOR ESSENTIAL AND MALIGNANT HYPERTENSION AND HYPERTENSION ASSOCIATED WITH CHRONIC PYELONEPHRITIS

JOHN L. NEWELL, M.D.,* AND REGINALD H. SMITHWICK, M.D.†

BOSTON

THE prognosis in pregnancy complicated by a pre-existing hypertension with or without renal disease is notoriously poor for both the mother and the infant. Corwin and Herrick,^{1 2} in their classic papers written in 1927, made the following statement:

Very few women who begin pregnancy with a blood pressure above 150 systolic or 100 diastolic can go through pregnancy successfully, that is with a living child. It is our opinion moreover, that pregnancy does much to accelerate the progress of chronic cardiovascular disease, that it may bring it out when latent and is to be avoided when the disorder has made evident inroads.

Severe hypertension of any origin is considered by many others to be a strong indication for therapeutic abortion. Watson³ regarded a pronounced hypertension with or without albuminuria as an indication for the induction of abortion. Fishberg⁴ observed that the pregnancy should be terminated if the blood pressure continued to rise or evidence of cardiac or renal insufficiency appeared.

In the 14 cases reported below all the patients had arterial hypertension, the blood pressures averaging 196 systolic, 130 diastolic, on admission prior to splanchnicectomy. For the most part the prenatal care and deliveries were conducted by obstetricians in the localities in which the patients resided. The blood-pressure reactions were studied by the postural and cold test in the first trimester and in most cases at seven months of pregnancy and at six weeks post partum.

As might have been expected with this type of case, the average age at delivery was thirty-one years. The average parity was 2.3. The time elapsing between the diagnosis of hypertension and the splanchnicectomy averaged seventy-five months, and the time between splanchnicectomy and the pregnancy studied averaged thirty-one months,

with the exception of a case in which splanchnicectomy was performed during the first trimester. The blood pressure following splanchnicectomy prior to the pregnancies averaged 135 systolic, 87 diastolic, and only 2 patients had persistent albuminuria.

The nature of the hypertension is of interest. Seven patients were classified preoperatively as having so-called "essential hypertension." Three gravida I's and 2 gravida II's, all without demonstrable kidney disease, were known to have had hypertension prior to their pregnancies. One gravida III and 1 gravida V, also without demonstrable kidney disease, developed hypertension during the second and first pregnancies respectively. Two gravida I's and 2 gravida II's were classified as having essential hypertension and associated chronic pyelonephritis, the presence of the latter being proved by renal studies, by gross inspection of the kidneys at operation and by biopsies taken from the kidneys. Two gravida II's developed both hypertension and pyelonephritis during the first pregnancies. The 2 remaining patients in this group developed renal disease and hypertension prior to their pregnancies. There were 3 cases of malignant hypertension, with pyelonephritis in 2. In a gravida II the disease began two years after the first pregnancy, another gravida II had had eclampsia during her first pregnancy six years earlier and known hypertension for two years, and in a gravida V the disease had become manifest during her third pregnancy. Thus, in all cases, hypertension antedated the pregnancies under discussion, and in 3 cases previous pregnancies had been interrupted because of hypertension.

In 9 cases the blood pressure during pregnancy remained within normal limits, and there was no albuminuria. The other 5 patients showed no significant elevation of blood pressure until the third trimester, when 2 developed marked elevation (above 180 systolic). In one of these cases a

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Hospital and Union Memorial Hospital 8th, cloth, 253 pp
New York W W Norton and Company, Incorporated,
1947 \$3 00

In this popular book, Dr Bernheim, noted for his work on transfusion and the vascular system, writes about surgery and surgeons on the basis of his own life and experiences. The story is written in a charming narrative style covering various aspects of the practice of surgery and high lighting the daily life, trials and tribulations of the surgeon. This narrative should find a place in the libraries of surgeons and in collections of light reading for medical students and in medical-history collections.

Principles and Practice of Obstetrics By Joseph B De Lee, M.D., and J P Greenhill, M.D., attending obstetrician and gynecologist, Michael Reese Hospital, obstetrician and gynecologist, associate staff, Chicago Lying-In Hospital, chairman, Department of Gynecology, Cook County Hospital, and professor of gynecology, Cook County School of Medicine. Ninth edition 4th, cloth, 1011 pp, with 1108 illustrations, 211 in color Philadelphia W B Saunders Company, 1947 \$10 00

This authoritative treatise, first published in 1913 by the late Dr De Lee, has been thoroughly revised and practically rewritten by Dr Greenhill. New chapters have been added on minor disturbances of pregnancy, premature labor, prolonged pregnancy or post-maturity and missed labor, fetal erythroblastosis, care of premature babies, circumcision and pemphigus neonatorum. The chapters on physiology of the fetus and ante-partum and post-partum care have been replaced by new ones. Additional material has been added to the subject of analgesia and anesthesia, including detailed information on direct, local and infiltration anesthesia, and caudal anesthesia. New material has been added to the sections on diseases of the blood and on surgical operations. New material has also been incorporated in the chapters on hyperemesis gravidarum, toxemias of pregnancy, post-partum hemorrhage, placenta previa, abruptio placentae, placenta accreta and acute and chronic infectious diseases complicating pregnancy. Detailed information is given on the use of penicillin and the sulfonamides, and the importance of German measles in obstetrics is emphasized.

Many new illustrations have been added, and a bibliography covering all references in the text is appended to each chapter. The illustrations are excellent, the text is well printed with a good type on good paper. A good index concludes the volume. This book is recommended for all medical libraries and the libraries of physicians practicing obstetrics.

NOTICES

JOSEPH H PRATT DIAGNOSTIC HOSPITAL

30 Bennet Street, Boston
Lecture Hall, 9-10 a m

MEDICAL CONFERENCE PROGRAM

- Wednesday, June 4 — Chemotherapy of Hodgkin's Disease and Leukemia Dr Louis Weisfuse
Friday, June 6 — Intracranial Aneurysms Dr William Sweet
Wednesday, June 11 — Treatment of Hyperthyroidism Dr Willard Vander Laan
Friday, June 13 — A Summary of Congenital Heart Disease Dr Sidney Farber
Wednesday, June 18 — Pediatric Clinicopathological Conference Drs James M Baty and H E MacMahon
Friday, June 20 — Hormonal Alteration of Advanced Carcinoma of the Breast Dr Ira Nathanson
Wednesday, June 25 — Reginald Heber Fitz's Contribution to Acute Appendicitis and Acute Pancreatitis Dr Hyman Morrison
Friday, June 27 — Ideology and Management of Hemoglobinuric Nephrosis Dr C H Burnett

On Tuesday and Thursday mornings, Dr S J Thannhauser will give medical clinics on hospital cases. On Saturday mornings, clinics will be given by Dr William Dameshek. Medical rounds are conducted each weekday by members of the staff from 12 00 to 1 00 in the lecture hall.

All exercises are open to the medical profession.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the of the New England Hospital for Women and Children be held on Thursday, June 5, at 7 15 p m, in the class of the Nurses' Residence. Dr Allan M Butler will discuss the subject "Parenteral Fluid Therapy with Potassium Solution." Dr Eleanore C Zaudy will be chairman.

NORTON MEDICAL AWARD

W W Norton and Company is again offering the Norton Medical Award for book manuscripts written for the public by professional workers in the field of medicine. Terms of the award have been slightly altered. The publishers now set no final closing date for the submission of manuscripts, which may be submitted at any time, the award not being limited to any one year. The Norton Medical Award offers \$5000 as a guaranteed advance against royalty. Either complete manuscripts or a detailed table of contents together with one hundred pages of manuscript may be submitted. A descriptive folder giving full details of the terms of the award may be secured on request from the publisher W W Norton and Company, Incorporated, 101 Fifth Avenue New York 3, N Y.

Books that have previously won the Norton Medical Award are *The Doctor's Job*, by Carl Binger, M.D., *Doctors in Doctors' West*, by Edward H Hume, M.D., and *A Surge Domain*, by Bertram M Bernheim, M.D.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JUNE 5

THURSDAY JUNE 5

7 15 p m Clinical Conference and Staff Meeting Nurses' Residence, New England Hospital for Women and Children

FRIDAY JUNE 6

*9 00-10 00 a m Intracranial Aneurysms Dr William Sweet
Joseph H Pratt Diagnostic Hospital

*10 00 a m-12 00 m Medical Staff Rounds Peter Bent Brigham Hospital

MONDAY JUNE 9

*12 15-1 15 p m Clinicopathological Conference Peter Bent Brigham Hospital

TUESDAY JUNE 10

*12 15-1 15 p m Clinicoradiological Conference Peter Bent Brigham Hospital

WEDNESDAY JUNE 11

*9 00-10 00 a m Treatment of Hyperthyroidism Dr Willard Vander Laan Joseph H Pratt Diagnostic Hospital

*11 00 a m-12 00 m Medical Clinic Amphitheater Children's Hospital

*12 00 m Clinicopathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital

*2 00-3 00 p m Combined Clinic by the Medical Surgical and Orthopedic Services Amphitheater Children's Hospital

*Open to the medical profession

JUNE 1-7 American Board of Obstetrics and Gynecology Page 7 issue of May 15

JUNE 4-27 Medical Conference Program Joseph H Pratt Diagnostic Hospital Notice above

JUNE 5 New England Hospital for Women and Children Notice above

JUNE 5-8 American College of Chest Physicians Page 418 issue of March 13

JUNE 6-8 American Heart Association Page xvii issue of May 8

JUNE 7 AND 8 American Society for the Study of Sterility Page 31 issue of February 20

JUNE 9-13 American Medical Association Page 698 issue of November 7

JUNE 11 Harvard Medical Alumni Association Page 646 issue of April 24

JUNE 11 Tufts Medical Alumni Dinner Page 646 issue of April 24

JUNE 16-18 New England Health Institute Page 816 issue of May

JUNE 30-JULY 3 American Urological Association Hotel Statler Buffalo

SEPTEMBER 2-6 American Congress of Physical Medicine Page 6 issue of April 17

SEPTEMBER 2-7 International Cancer Research Congress Page 3 issue of February 27

SEPTEMBER 8-12 Third American Congress on Obstetrics and Gynecology Page 340 issue of February 27

OCTOBER 6-10 American Public Health Association Page 456 issue of March 20

CASE 2. This patient was 20 years of age at the time of her final admission in November, 1940. At the age of 4 she had been admitted for a urinary-tract infection and had subsequently been followed in the Out Patient Department. During the 3 years prior to splanchnicectomy she had been admitted to the hospital twice because of urinary-tract infections caused by an organism of the colon-bacillus group. This infection responded to chemotherapy, and the urine became intermittently sterile. The blood pressure had always been elevated, and during this period the hypertension became progressively severer and the eye-ground changes progressively more marked. The family history was noncontributory.

On final admission the blood pressure was 205/140, and the range during postural and cold tests was from 205/150 to 174/110. The eye grounds showed Grade II changes, both spastic and sclerotic. The heart was normal in size and slightly altered in shape. The nonprotein nitrogen was 26 mg per 100 cc, a phenolsulfonephthalein test showed 15 per cent excretion of the dye in 15 minutes and 50 per cent in 2 hours. The maximum urinary concentration was 1012. There was a +++ test for albumin, and the sediment contained a few to many white cells. Cultures of the urine showed abundant growth of nonhemolytic streptococci. Intravenous pyelograms were not remarkable. On sedation the blood pressure fell to 145/100.

On November 20 the first stage of a lumbodorsal splanchnicectomy was performed, the sympathetic trunk on the left being removed from the tenth dorsal to the second lumbar segment inclusive. The second stage was performed on December 3, the sympathetic trunk being removed from the tenth dorsal to the first lumbar inclusive. The great splanchnic nerves were removed on both sides from the celiac ganglia to the midthoracic level. At operation both kidneys were found to be irregularly scarred, contracted and lobulated, a finding typical of chronic pyelonephritis. Biopsies taken from both kidneys showed typical chronic pyelonephritis and chronic vascular nephritis, Grade III. The patient was discharged on December 16, the blood pressure being 133/104. Two years after the splanchnicectomy the blood pressure was 109/82.

The patient became pregnant for the first time 3½ years after operation, the blood pressure being 128/94 and the urine containing no albumin. During the 6th month of pregnancy the blood pressure was 122/88, but at 34 weeks a blood pressure of 170/110 developed and the urine showed a +++ test for albumin. She was delivered by cesarean section of an infant weighing 3 pounds, 9 ounces, who survived. Two months post partum and 51 months after operation the blood pressure was 138/94.

CASE 3. A 28-year-old gravida I was admitted in May, 1942, for hypertension. For 15 years she had had headaches associated with vomiting. Nine years previously she was found to have a slightly elevated blood pressure, and 18 months prior to admission the blood pressure was 180/120. Both parents, who were 49 and 56 years of age, had hypertension.

The blood pressure on admission was 180/130, the range during postural and cold tests being 198/140 to 148/88. The retinal vessels showed spasm. The heart was normal in size and shape. An electrocardiogram was within normal limits. The nonprotein nitrogen was 26 mg per 100 cc. A phenolsulfonephthalein test showed 32 per cent excretion of the dye in 30 minutes and 65 per cent in 2 hours. The urine, which concentrated to 1026, gave a + test for albumin, and the sediment contained 10 white cells per high-power field. On June 1 the first stage of a lumbodorsal splanchnicectomy was performed, with removal of the sympathetic trunk from the ninth dorsal to the third lumbar segment, inclusive, on the right. Two weeks later, at a similar operation, the sympathetic trunk on the left side was removed from the ninth dorsal to the second lumbar inclusive. The great splanchnic nerves were removed on both sides from the celiac ganglia to the midthoracic level. Biopsies of the kidney were reported as showing a chronic vascular nephritis, Grade II. After an uneventful convalescence the patient was discharged with a blood pressure of 140/100.

In August, 1943, she became pregnant. The pregnancy was uneventful, the blood pressure varying between 120/84 and 185/120 and the urine remaining free of albumin. At the 30th week of pregnancy she was checked at the hypertension

clinic and found to have a blood pressure of 138/90. Three hours later she experienced massive vaginal bleeding.

On admission to the hospital the blood pressure was 180/120, and the urine gave a +++ test for albumin. The uterus was firm and did not relax. A diagnosis of premature separation of the placenta was made. Since the fetal heart beat disappeared 20 minutes after admission, the membranes were ruptured and labor was stimulated with minimal doses of Pitocin. Ten hours later a stillborn, premature infant was delivered by low forceps. The placenta was completely separated, and the uterus was filled with large blood clots. The patient suffered moderate shock and required two transfusions during labor. She was discharged on the 13th postpartum day, when the blood pressure was 148/98.

The patient experienced a second pregnancy, which terminated successfully in March, 1945, with a normal delivery of a living infant weighing 4 pounds, 4 ounces. This delivery was also complicated by premature separation of the placenta. During pregnancy the blood pressure averaged 155/105, and the urine remained free of albumin. Labor was painless until the head distended the perineum.

CASE 4. A 28-year-old gravida I had first been known to have hypertension when she was 15 years old. The blood pressure at times was recorded as over 200 systolic. The admission blood pressure was 205/150, the range during postural and cold tests being 205/154 to 148/110. The eye grounds were classified as Grade I. A 7-foot plate showed the heart to be normal in size and shape. The electrocardiogram was normal. The nonprotein nitrogen was 28 mg per 100 cc. A phenolsulfonephthalein test showed 30 per cent excretion of the dye in 15 minutes and 93 per cent excretion in 2 hours. The urine, which concentrated to 1022, gave a + test for albumin, the sediment was normal, as was an intravenous pyelogram. On sedation the blood pressure fell to 138/110.

In February, 1944, the first stage of a bilateral lumbodorsal splanchnicectomy was performed, the left sympathetic trunk being removed from the eighth dorsal to the first lumbar segment, inclusive. Two weeks later the second stage was performed, the right sympathetic trunk being removed from the seventh dorsal to the second lumbar inclusive. The great splanchnic nerves were removed on both sides from the celiac ganglia to the midthoracic level. A renal biopsy showed a chronic vascular nephritis, Grade III.

Three months later, when the patient became pregnant, the blood pressure was 140/100, and the urine was normal. At 7 months the sediment contained white cells in clumps. This cleared with sulfadiazine therapy. At 34 weeks the blood pressure was 160/104, and 2 weeks later it rose to 190/128. The patient remained at bed rest in the hospital until the 40th week of pregnancy, when she started in labor spontaneously and was delivered normally of a living infant. For the 4 weeks prior to delivery while at bed rest she had had no complaints, and the urine had remained free of albumin. The blood pressure varied widely, averaging 170/120. On several occasions it reached 180/130, but a few hours later was found to be 126/90. Following delivery the blood pressure continued to be labile and was 170/110 when the patient was discharged. Eight months post partum the reading was 106/96 with the patient in the horizontal position. It could be raised to 160/118 when she was standing and stimulated by cold.

CASE 5. A 28-year-old gravida II was admitted in May, 1942, with a diagnosis of malignant hypertension. Ten years previously she had experienced a normal pregnancy. Three years later she began having headaches, which became progressively severer.

The blood pressure on admission was 245/140, the range during postural and cold tests being 250/170 to 196/132. The eye grounds showed hypertensive retinopathy with papilledema. A 7-foot heart plate showed definite enlargement. The heart was altered in shape, and the aorta was tortuous. An electrocardiogram was consistent with hypertensive heart disease. The nonprotein nitrogen was 33 mg per 100 cc. A phenolsulfonephthalein test showed 15 per cent excretion of the dye in 15 minutes and 15 per cent in 2 hours. The urine showed a specific gravity of 1012, with a ++ test for albumin, and the sediment contained rare red cells. Intravenous pyelograms were normal. On sedation the blood pressure fell to 150/110.

++++ test for albumin necessitated interruption of the pregnancy at the thirty-fourth week. Three cases showed only moderate hypertension (blood pressures below 160 systolic, 90 diastolic), but 1 of these patients, who had developed a premature separation of the placenta in her first pregnancy, successfully completed her second pregnancy after the termination of the study. In this group there were normal deliveries in 11 cases and cesarean sections in 3, the indication being a previous hys-

terectomy. The conservative and wisest procedure was to terminate the pregnancy. In view of our previous experience with pregnancy following splanchnicectomy, however, the consultant agreed to postpone abortion until the results of the splanchnicectomy could be determined, since in our opinion this latter procedure was indicated regardless of the pregnancy.* The family history revealed that the patient's mother had died of kidney disease.

The blood pressure on admission was 180/120, and the range during postural and cold tests was 138/106 to 204/144. The eye grounds were normal. A 7-foot heart plate was consistent with hypertension. An electrocardiogram and the nonprotein nitrogen were normal. A phenolsulfonephthalein

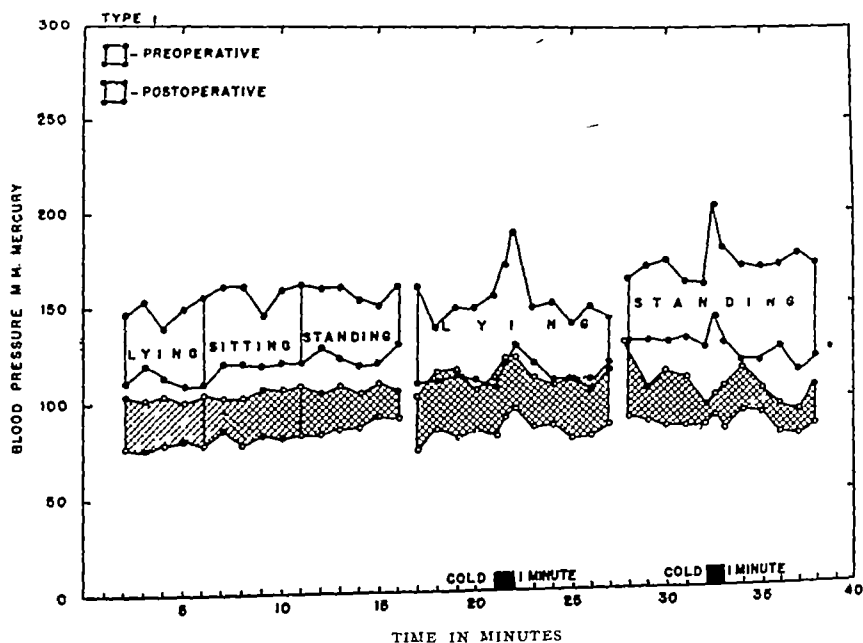


FIGURE 1 Case 1

This chart shows the blood-pressure levels before lumbodorsal splanchnicectomy and ten months later, one month after delivery. The postural and "cold" blood-pressure readings are compared. In recording these, readings are taken every minute for five minutes with the patient lying, sitting and standing. A cold test is then performed with the patient lying and is repeated with the patient standing. The postoperative (post-partum) range is shaded. This patient was six weeks pregnant when the splanchnicectomy was performed.

terotomy in 2 cases and fulminating pre-eclampsia in another. Thirteen babies are living and well—2 were delivered prematurely. One infant was still-born owing to premature separation of the placenta. The puerperium was uncomplicated in all cases except for the patient in Case 11, who developed a post-partum psychosis. The average blood pressure was 134 systolic, 89 diastolic, at two weeks post partum and 133 systolic, 87 diastolic, at six or more weeks post partum. None of the patients had albuminuria at that time.

The following are brief abstracts of the case reports.

CASE 1. A 24-year-old gravida II had first been seen in the 9th month of her first pregnancy with a blood pressure of 168/110 but no albuminuria. The blood pressure remained in this range for the remainder of this pregnancy, and the patient was delivered at term of a living infant. She was next seen 3 years later with a blood pressure of 186/120. The blood pressure continued to rise during the next 6 months, when she was admitted to the hospital. At that time the patient was 6 weeks pregnant. The consultant from the hypertensive clinic and the obstetric consultant believed that

test showed 45 per cent excretion of the dye in 15 minutes and 65 per cent in 2 hours. The urine concentrated to 1020 and contained no albumin, and the sediment was normal, as was an intravenous pyelogram. On sedation the blood pressure fell to 120/50. The Aschheim-Zondek test was positive.

On July 1, 1944, the first stage of a bilateral lumbodorsal splanchnicectomy was performed, with removal of the sympathetic trunk from the eighth dorsal to the third lumbar segment inclusive. Two weeks later a similar operation was performed on the left side, with removal of the sympathetic trunk from the eighth dorsal to the second lumbar segment inclusive. The great splanchnic nerves were removed on both sides from the celiac ganglions to the midthoracic level. Renal biopsies revealed chronic vascular nephritis, Grade II. The patient experienced an uneventful convalescence, and at discharge the blood pressure was 110/80.

During the remainder of this pregnancy the blood pressure was 110/70 to 104/90. There were no signs or symptoms of toxemia, and the urine was consistently free of albumin. On January 24, 1945, the patient was delivered of a living infant. The blood pressure during the puerperium varied between 102/60 and 130/100. At two subsequent post-partum visits the blood pressure was 128/78 and 132/80. Three months post partum the blood pressure was 120/80, and a month later it was 102/78. Blood-pressure data as revealed by the postural and cold tests are presented in Figure 1.

*In general we believe that the best results are obtained when the pregnancy follows the splanchnicectomy by at least twelve months. There may be a group of patients such as this one, however, in whom operation could be performed in the first trimester.

of blood pressure was detected. A year later the patient lost 25 pounds and suffered headaches that became worse during the 2 or 3 years preceding admission.

The blood pressure on admission was 225/130, the range during postural and cold tests being 226/146 to 184/114. The eye grounds were classified as Grade II. A 7-foot plate showed the heart to be normal in size and slightly altered in shape, the aorta being slightly tortuous. An electrocardiogram was normal. The nonprotein nitrogen was 26 mg per 100 cc and a phenolsulfonephthalein test showed 32 per cent excretion of the dye in 15 minutes and 55 per cent in 2 hours. The urine concentrated to 1019, gave a + test for albumin and contained a slightly abnormal sediment. Intravenous pyelograms were normal. On sedation the blood pressure fell to 122/80.

On November 22 the first stage of a lumbodorsal splanchnicectomy was performed. The sympathetic trunk was removed from the second dorsal to the first lumbar segment, inclusive. At a similar operation 2 weeks later the right trunk was removed from the ninth dorsal to the first lumbar. The great splanchnic nerves were removed from the celiac ganglions to the midthoracic level. The patient was discharged on December 13, the blood pressure ranging between 152/104 and 166/114.

She was readmitted for study in March, 1942, at which time she had no complaints. The blood pressure was 150/90 on admission but dropped to 110/94 with bed rest, the range being 150/90 to 80/40. The eye grounds were classified as Grade II. The cardiac status was considered normal. The renal blood flow (as measured by the Diodrast-clearance method) was 640 cc. per minute, or about two thirds normal.

The patient became pregnant in 1943. This pregnancy was uneventful throughout, with no signs or symptoms of toxemia and with delivery of a living infant at term. Two months post partum (62 months after operation) the patient was studied again. The blood pressure on admission was 122/82, and the range was from 164/114 to 128/88. An electrocardiogram and the kidney function tests were normal, and the eye grounds were completely normal.

CASE 8. A 31-year-old gravida III was first seen at the age of 29 years. She complained of severe headaches of 7 years' duration and had had known hypertension for 6 years. The family history was strongly positive for hypertensive disease. One year prior to admission she was delivered of a living child, the pregnancy being induced at 36 weeks because of a blood pressure of 230/120 and albuminuria. The puerperium was complicated by ptylitis. Four months before admission a therapeutic abortion had been performed.

On admission the blood pressure was 150/100, the range during postural and cold tests being 124/90 to 150/116. The heart was normal in size and shape, and the aorta was not tortuous. An electrocardiogram was normal, and the eye grounds were reported as showing Grade I changes. The specific gravity of the urine was 1.018, and there was no albumin; the sediment was normal. The nonprotein nitrogen was 20 mg per 100 cc. Intravenous pyelograms were normal except that there was slight evidence of pyelonephritis on the right side. On sedation the blood pressure fell to 110/78.

On March 19, 1943, the left sympathetic trunk was removed from the eighth dorsal to the second lumbar segment inclusive. On April 4 the right sympathetic trunk was removed from the ninth dorsal to the second lumbar inclusive. The great splanchnic nerves were removed on both sides from the celiac ganglions to the midthoracic level. Biopsies of the kidneys were reported as showing a Grade I chronic vascular nephrosis on the right and a Grade II chronic vascular nephrosis on the left.

The patient became pregnant 27 months after operation. At that time the blood pressure was 138/80, and the urine negative for albumin. The pregnancy was entirely normal throughout, the blood-pressure range being 120/78 to 140/90 and the urine consistently negative for albumin. An infant weighing 6 pounds, 3 ounces, was delivered normally in March 1946, after a short painless labor. Two weeks post partum the blood pressure was 120/80, and the urine normal.

CASE 9. A 32-year-old gravida III was admitted in March 1942, for hypertension. Nineteen months previously she had consulted a physician for prenatal care and had been found to have a systolic blood pressure of 200. Headache was the prominent symptom during this pregnancy, which terminated

normally, at term. Headache and tinnitus had subsequently persisted. The first pregnancy, 10 years previously, was believed to have been normal. The patient's mother had hypertension, and her father had died of a cerebral accident.

The blood pressure on admission was 190/110, the range during postural and cold tests being 190/140 to 158/102. The eye grounds showed narrowing of the retinal arteries. A 7-foot plate revealed the heart to be slightly altered in size and shape and the aorta to be tortuous. An electrocardiogram was within normal limits. The nonprotein nitrogen was 18 mg per 100 cc., and a phenolsulfonephthalein test showed 15 per cent excretion of the dye in 15 minutes and 75 per cent in 2 hours. The urine concentrated to 1028 and gave a ++ test for albumin, and the sediment showed rare red cells. Intravenous pyelograms showed prompt excretion and normal kidneys. On sedation the blood pressure fell to 128/90.

On March 23 the first stage of a bilateral lumbodorsal splanchnicectomy was performed on the right, the sympathetic trunk from the ninth dorsal to the third lumbar segment inclusive being excised. An identical operation was performed on the left 2 weeks later. The great splanchnic nerves were removed from the celiac ganglions to the midthoracic level on both sides. Reports of the biopsies from the kidneys revealed a Grade III chronic vascular nephrosis.

The patient became pregnant in July, 1943 and was readmitted in October for study and for a decision regarding the advisability of abortion. She complained of easy fatigability and nocturnal dyspnea. The blood pressure was 155/105 on admission but became normal during the hospital stay. The urine concentrated to 1030 and gave a + test for albumin, and the sediment contained occasional white cells. A phenolsulfonephthalein test showed 65 per cent excretion of the dye in 2 hours and the nonprotein nitrogen was 20 mg per 100 cc. It was decided that the pregnancy should be allowed to continue. The course of the pregnancy was uneventful, the blood pressure remaining below 155/100, the urine gave a + test for albumin or less. A female infant weighing 7 pounds, 10 ounces was delivered on March 10, 1944, following a normal labor.

CASE 10. A 34-year-old gravida II had first been seen in May, 1936, when she was 25 years old and single. Her complaints were headache and loss of vision. For 8 years she had had headaches that had become progressively severer. Eighteen months prior to admission she had been refused life insurance because of a systolic blood pressure of 170. The amaurosis had been present for 2 weeks. The patient's mother had died of cerebral hemorrhage, and an aunt of hypertensive disease.

The blood pressure on admission was 230/140. The heart was enlarged and abnormal in size and shape. An electrocardiogram showed slight changes, with left-axis deviation. The eye grounds were classified as Grade III and showed albuminuric retinitis. The patient could not distinguish fingers at 3 feet. The nonprotein nitrogen was 25 mg per 100 cc. A phenolsulfonephthalein test showed 18 per cent excretion of the dye in 15 minutes and 56 per cent in 2 hours. The urine concentrated to 1016 and showed a ++ test for albumin, and the sediment contained white cells in clumps and an occasional granular cast. The uterus was consistent with a 7½ months' pregnancy. The pregnancy was interrupted by an abdominal hysterotomy, a normal living female infant weighing 4 pounds, 8 ounces, being delivered.

Three months later the blood pressure was 158/100 and this dropped to 140/90 with bed rest. The urine concentrated to 1016 and gave a +++ test for albumin, and the sediment contained hyaline and granular casts.

In December the patient was readmitted with a blood pressure of 165/110. A two-stage operation was performed, the sympathetic trunk from the tenth to the twelfth dorsal segment, inclusive, being removed on each side. The great splanchnic nerves were removed on both sides from the celiac ganglions to the mid-thoracic level. The convalescence was uneventful.

Six years later the patient became pregnant for the second time. The blood pressure during the pregnancy varied between 140/80 and 120/80. The patient was symptom free and in good health throughout. The urine was free of albumin until the 7th month, when it gave a + test for albumin and the sediment showed white cells in clumps, which however, responded to sulfadiazine therapy. Two weeks prior to term

On May 9 the first stage of a lumbodorsal splanchnicectomy was performed, the right sympathetic trunk being removed from the ninth dorsal to the second lumbar segment, inclusive. The same operation was repeated on the left side two weeks later. The great splanchnic nerves were removed on both sides from the celiac ganglions to the midthoracic level. At operation the kidneys were noted to be scarred and contracted in an irregular fashion. Renal biopsies showed a Grade II chronic vascular nephritis on the left and a Grade III on the right. The patient was discharged on June 17, the blood pressure being 137/116.

Fourteen months after operation she was readmitted for study. Nausea and occasional dyspnea were the only symp-

urinary concentration was 1 027, with a + test for albumin, and the sediment was normal. Intravenous pyelograms were normal. On sedation the blood pressure fell to 132/90.

On April 1 the first stage of a splanchnicectomy* was performed, the left sympathetic trunk being excised from the tenth dorsal to the twelfth dorsal segment, inclusive. The same operation was performed on the right side 10 days later. The great splanchnic nerves were removed from the celiac ganglions to the midthoracic level. The patient was discharged on April 22 with a blood pressure of 115/86. She was seen at intervals during the next 4 years. The postoperative blood pressures were as follows: at 2 months, 120/80, at 5 months, 110/80, at 16 months, 108/80, at 24 months, 110/80;

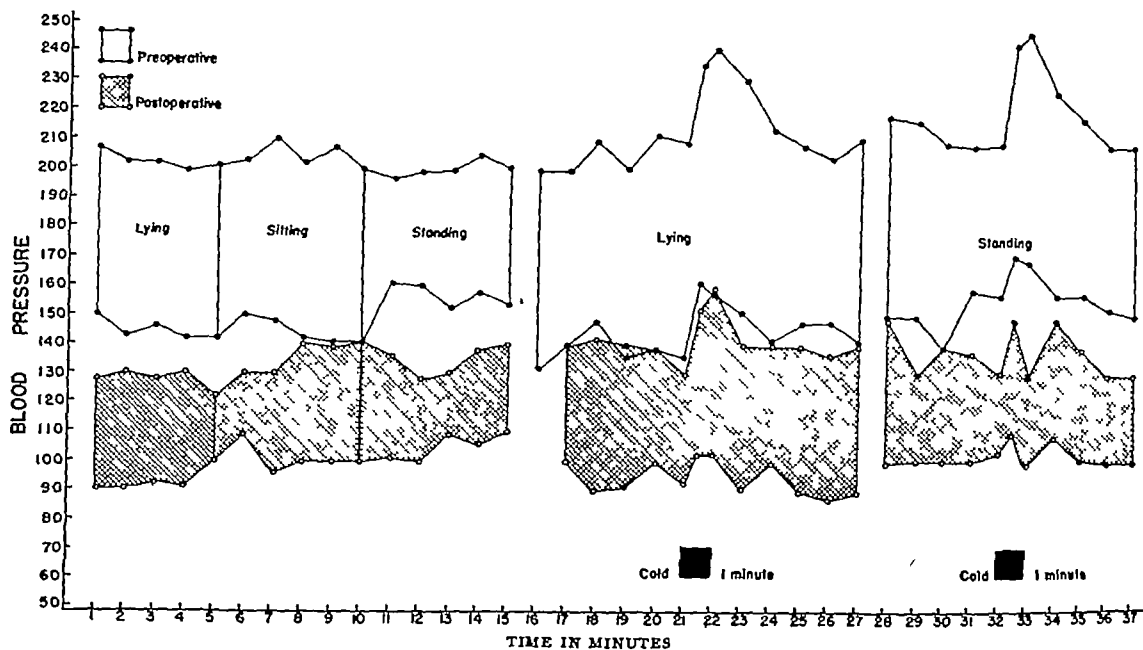


FIGURE 2 Case 5 -

The blood pressure readings before lumbodorsal splanchnicectomy for malignant hypertension, associated with chronic bilateral pyelonephritis, are compared with those made fourteen months later (range shaded), at which time the patient was in the second month of pregnancy, whose subsequent course was uneventful.

toms. The blood pressure on admission was 132/90, the range during postural and cold tests being 158/110 to 120/106. A phenolsulfonephthalein test showed 55 per cent excretion of the dye in 2 hours. The nonprotein nitrogen was 16 mg per 100 cc, and the urine showed a specific gravity of 1.016 and a + test for albumin. In addition to the marked improvement in the blood pressure the heart had decreased in size, and the electrocardiogram showed a striking improvement with return to normal of the ST segments and T waves. The eye grounds showed minimal residual changes and were classified as Grade I.

The patient had become pregnant 1 year after operation. The pregnancy was uneventful, and she was delivered at term of a living infant, the blood pressure rising to 160/110 during labor (Fig. 2).

CASE 6. A 29-year-old gravida II had first been seen in March, 1937, at the age of 20 years. She had had known hypertension since her 12th year. During childhood she had had kidney trouble, the details of which were not known. For the previous eight years the blood-pressure range had been 182/112 to 240/116. The symptoms consisted of headaches of increasing severity, nervousness, vertigo and increasing fatigability.

The blood pressure on admission was 170/120, the range during postural and cold tests being 176/116 to 240/160. A 7-foot plate showed the heart to be normal in size and shape. The electrocardiogram was normal, as were the eye grounds. The nonprotein nitrogen was 24 mg per 100 cc. A phenolsulfonephthalein test showed 25 per cent excretion of the dye in 15 minutes and 62 per cent in 2 hours. The maximum

at 27 months, 129/90, at 42 months, 126/94, and at 50 months, 122/85.

The patient first became pregnant during the 6th year after operation. She was followed in this pregnancy through the 26th week, the blood pressure did not exceed 104/60, and the urine was normal. The patient was not seen for the remainder of this pregnancy, which resulted in a stillbirth, the details of which are not known.

The patient was next seen 8 years after operation during her second pregnancy, when she was 29 years old. The blood pressure during this pregnancy was as follows: at 4 months, 112/64, at 5 months, 100/70, at 6 months, 114/80, at 7 months, 110/60, and at 8 months, 126/68. The urine was negative for albumin throughout this pregnancy. A 7-pound female infant was delivered spontaneously on July 7, 1945. Six and 11 weeks post partum the blood pressures were 136/88 and 120/82 respectively.

CASE 7. A 29-year-old gravida I was first seen in 1938, when she was 24 years of age and single. Seven years previously, during a routine physical examination, an elevation

*In this case and in Case 10 a lower thoracic sympathectomy and splanchnicectomy were performed. These patients were operated on prior to October, 1938, when lumbodorsal splanchnicectomy was adopted as routine for hypertension. These were 2 of a few excellent results that one of us (R. H. S.) has noted following this operation for hypertension. Peet¹ reported the case of a patient with malignant hypertension who responded well to an operation of this type. The blood pressure of his 22-year-old patient prior to operation ranged from 230/170 to 280/190. Eight months later it was 136/90. The patient became pregnant 14 months after operation. Two months later the blood pressure rose to nearly preoperative levels and an abortion was performed. Four years and two months after operation the patient was well and the blood pressure was 139/101.

She was next seen in June, 1942, when she was 24 weeks pregnant. At that time a Diodrast-clearance test showed a marked reduction in renal blood flow to about a third of normal. The blood pressure was 132/92, and the urine was normal. The pregnancy continued uneventfully until the 4th week, when the blood pressure rose to 152/110 and the weight had increased to 234 pounds. The patient was admitted to the Boston Lying-in Hospital for study. The blood pressure responded well to bed rest (Fig. 3). The urea clearances during the 37th week of pregnancy showed 99 per cent and 104 per cent excretion of the dye respectively. During the following week the blood pressure rose to 164/120 and the urine showed a ++ test for albumin. Labor was induced by rupture of the membranes, and an infant weighing 6 pounds, 3 ounces, was delivered normally. Two and 6 weeks post partum the blood pressure was 110/84 and 122/84 respectively. The patient was evaluated 3 months after delivery when the blood pressure was 120/68, the range during postural and cold tests being 110/80 to 150/130. When she was admitted for study 34 months later the blood pressure was 176/118, the range being 146/110 to 210/164. The eye grounds showed marked improvement and were classified as Grade 1. An electrocardiogram was also improved and was reported as normal. At that time the patient weighed 200 pounds.

CASE 13 A 37-year-old gravida I had first been seen at the age of 33 when she was single. Because of weight loss and easy fatigability she had consulted a physician, who had found hypertension and referred her to the hospital for study in May, 1941. The blood pressure on admission was 210/150, with an average of 195/110 when the patient was resting in bed. The heart shadow was within normal limits. An electrocardiogram showed normal rhythm, inverted T waves in Lead 3 and a normal Lead 4. The eye grounds showed slight tortuosity and arteriovenous nicking. Pyelograms disclosed good excretion of the dye through both kidneys within 5 minutes. The urine concentrated to 1018 and contained no albumin, and the sediment was normal. A phenolsulfonphthalein test showed 35 per cent excretion of the dye in 20 minutes and 45 per cent in 1 hour. On sedation the blood pressure fell to 180/110. The patient was discharged with the diagnosis of essential hypertension.

In November, 1942, she was readmitted for splanchnicectomy. The laboratory data were essentially the same as those on the previous admission. A urea clearance showed a maximum excretion of 60 per cent with a volume of 145 cc. and of 68 per cent with a volume of 280 cc.

On December 1 a left lumbodorsal splanchnicectomy was performed, with excision of the sympathetic trunk from the tenth dorsal to the second lumbar segment, inclusive. On December 13 an identical operation was performed on the right side. On both sides the great splanchnic nerves were removed from the semilunar ganglions to above the mid-thoracic level. Biopsies taken from both kidneys revealed early renal arteriolar medial hyperplasia. After an uneventful convalescence the patient was discharged on January 11, 1943, with a blood pressure of 140/80.

The patient married in 1943 and became pregnant in December, 1944. The pregnancy was entirely normal. The highest blood pressure recorded was 138/85. The urine was consistently free of albumin, and the total weight gain was 18 pounds. She was delivered on October 9, 1945, of a living female infant and was discharged on the 14th post-partum day with a blood pressure of 132/90. Six weeks after delivery the blood pressure was 128/90.

CASE 14 A 39-year-old gravida V was admitted in January, 1943, complaining of headache and vertigo. She had developed hypertension during the first pregnancy 10 years previously. The hypertension had become progressively severer with three subsequent pregnancies.

Physical examination revealed an obese woman weighing 200 pounds. The blood pressure was 180/130, the range during postural and cold tests being from 170/106 to 218/132. The heart was not enlarged, but the aorta was tortuous. An electrocardiogram was normal. The urine showed a + test for albumin and a maximum concentration of 1020. The sediment was normal. The nonprotein nitrogen was 30 mg and the uric acid 2.9 mg per 100 cc., and the phenolsulfonphthalein test showed 30 per cent excretion of the dye in 15

minutes and 90 per cent in 2 hours. Intravenous pyelograms were normal. On sedation the blood pressure fell to 150/78.

On January 21 a right lumbodorsal splanchnicectomy was performed, the sympathetic trunk being removed from the ninth dorsal to the second lumbar segment, inclusive. On February 3 a similar operation was performed on the left, the sympathetic trunk being removed from the eighth dorsal to the second lumbar inclusive. The great splanchnic nerves were removed on both sides from the celiac ganglions to the mid-thoracic level. Biopsies taken at operation were reported as showing a Grade II chronic vascular nephritis. The patient was discharged on February 24 with a blood pressure of 155/105.

The patient conceived in December and experienced an uncomfortable pregnancy during which she gained 56 pounds. The blood pressure ranged between 150/70 and 150/90. The urine remained free from albumin. She was delivered on August 29, 1944, of a full-term, living infant. The blood pressure was 129/78, and the urine was normal when the patient was seen 18 months post partum.

Moderate to severe hypertension had been present in all cases until the patients had been treated by splanchnicectomy. Fourteen living infants were delivered, the oldest of which is now four years of age. One baby was stillborn, owing to premature separation of the placenta.

Three of the patients had so-called "malignant hypertension" prior to lumbodorsal splanchnicectomy. They responded favorably to operation and tolerated subsequent pregnancy well. Both mothers are living and well, having exceeded the average life expectancy for patients with malignant hypertension, and having living children. This experience is regarded as unique. In 1 case the pregnancy was completely uneventful, and in the other a transient rise in blood pressure associated with the occurrence of a + test for albumin necessitated delivery a few days prior to full term. In the third case the pregnancy was uneventful, but the puerperium was complicated by a psychosis.

The other 11 patients had severe essential hypertension, with or without chronic pyelonephritis. These patients are also living and well following pregnancy. The hypertension is much improved over that prior to splanchnicectomy. There is as yet no definite evidence that pregnancy has materially affected the postoperative course of the hypertensive process in these cases. In 5 cases increasing hypertension associated with increasing albuminuria occurred during the third trimester, necessitating delivery prior to full term. In no case did the hypertension increase prior to the seventh month of pregnancy.

It should be emphasized that in these cases, as in patients who have not had a previous lumbodorsal splanchnicectomy, one should not procrastinate when the signs of toxemia appear. The established and accepted criteria for termination of pregnancy should be closely observed.

It seems most unlikely that the majority of these patients could have obtained living children without suffering material cardiovascular damage or an increase in the severity of the hypertension following pregnancy had not lumbodorsal splanchnicectomy

the patient was delivered by a repeat hysterotomy of a female infant weighing 6 pounds, 5 ounces. The puerperium was uneventful. Six weeks post partum the blood pressure was 136/88, and the urine was free of albumin.

CASE 11 A 33-year-old gravida II was admitted in September, 1940, with the diagnosis of malignant hypertension and pyelonephritis. She had been known to have hypertension for 2 years. The family history was irrelevant. Six years before admission, in the 8th month of the first pregnancy, pyelitis, hypertension, coma and convulsions had developed. This pregnancy had been terminated by an abdominal hysterotomy at the 36th week. For 2 years prior to

months postoperatively, when the patient was 1 month pregnant, the blood pressure was 98/58, and the urine was normal. The pregnancy was entirely uneventful. The blood-pressure range was 115/80 to 150/98. The urine remained free of albumin, and the total weight gain was 17 pounds.

Sixty-four months after operation, when the patient was 2 weeks from term, a repeat hysterotomy was performed under spinal anesthesia. A female infant weighing 7 pounds was delivered. The surgical convalescence was uneventful, and the patient was discharged on the 14th postoperative day, the blood pressure being 120/84 and the urine free of albumin. Unfortunately, the patient manifested symptoms of a puerperal psychosis beginning on the 10th post-partum day. These

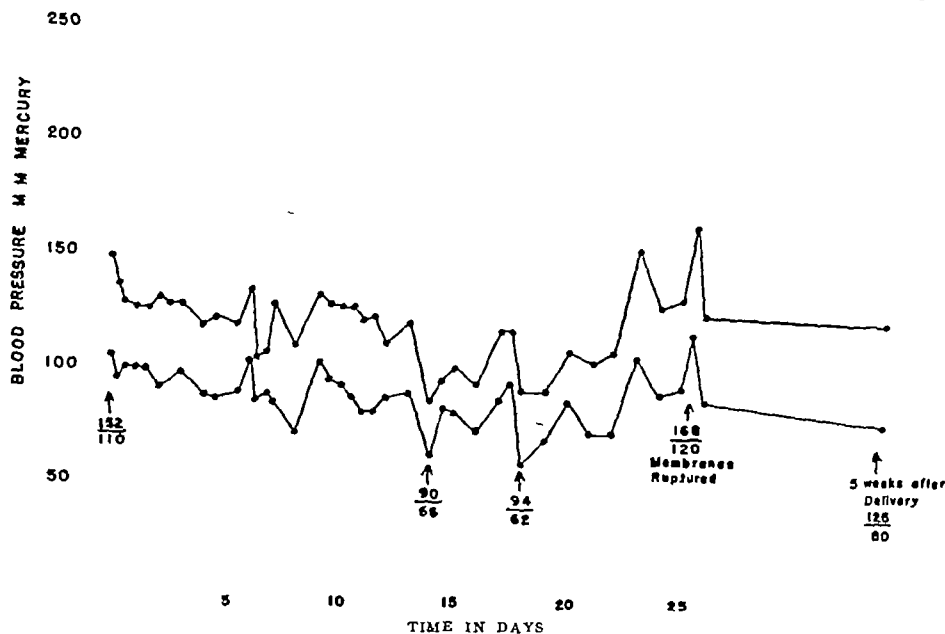


FIGURE 3 Case 12

The average blood-pressure levels are charted for twenty-six days prior to delivery. During that time the patient was hospitalized because of a reading of 152/110. She responded well to rest. The membranes were ruptured ten days prior to term because the blood pressure had risen to 168/120. Five weeks following delivery the level was 125/80. This patient had malignant hypertension prior to lumbodorsal splanchnicectomy.

admission the patient had had frequent headaches, tinnitus and transient paresthesias.

The blood pressure on admission was 240/150, the range during postural and cold tests being from 138/112 to 240/150. The heart was normal in size and shape. An electrocardiogram was typical of hypertension. The eye grounds showed marked hypertensive changes with hemorrhages, exudate and advanced changes in the retinal arteries and marked bilateral papilledema. The nonprotein nitrogen was 21 mg per 100 cc, and a phenolsulfonephthalein test showed 25 per cent excretion of the dye in 15 minutes and 55 per cent in 2 hours. The maximum urine concentration was 1030. There was a + test for albumin, and the sediment was normal. Intravenous pyelograms were normal. On sedation the blood pressure fell to 126/98.

The first stage of the splanchnicectomy was performed on October 2. The left sympathetic trunk was excised from the ninth dorsal to the second lumbar segment, inclusive. At the second stage, on October 16, the right sympathetic trunk was removed from the ninth dorsal to the first lumbar, inclusive. The great splanchnic nerves were removed on both sides from the celiac ganglions to the midthoracic level. No biopsies were taken, but at operation both kidneys were described as diffusely scarred and contracted in an irregular fashion, the gross appearance being characteristic of chronic pyelonephritis. The patient was discharged on October 30, when the blood pressure was 124/95.

Twenty-seven months after operation the blood pressure was 124/91, the range during postural and cold tests being 140/108 to 112/82. Eleven months later the blood pressure was 120/76, and the range 150/112 to 115/68. Fifty-five

months postoperatively, when the patient was 1 month pregnant, the blood pressure was 98/58, and the urine was normal. The pregnancy was entirely uneventful. The blood-pressure range was 115/80 to 150/98. The urine remained free of albumin, and the total weight gain was 17 pounds.

CASE 12 A 36-year-old gravida V was admitted in February, 1941, with a diagnosis of malignant hypertension which had developed during the third pregnancy in 1935. The fourth pregnancy had been interrupted at 4 months because of severe hypertension.

The blood pressure on admission was 206/130, the range during postural and cold tests being 164/110 to 220/160. The eye grounds showed changes indicative of the malignant phase of hypertensive disease. There were marked abnormalities of the retinal arteries, with occasional hemorrhages and associated papilledema. A 7-foot plate showed the heart to be enlarged and abnormal in shape, with a tortuous aorta. An electrocardiogram was consistent with mild hypertensive heart disease. The nonprotein nitrogen was 15 mg per 100 cc, and a phenolsulfonephthalein test showed 40 per cent excretion of the dye in 15 minutes and 75 per cent in 2 hours. The urine contained no albumin, and the sediment was normal, as were intravenous pyelograms.

On February 25, 1941, at the first stage of a lumbodorsal splanchnicectomy the sympathetic trunk from the tenth dorsal to the first lumbar segment, inclusive, was removed on the right. Two weeks later, at the second stage, the left sympathetic trunk from the ninth dorsal to the first lumbar, inclusive, was removed. Biopsies from both kidneys showed a chronic Grade II vascular nephritis. After a normal convalescence the patient was discharged on March 29, with a blood pressure of 135/95.

century, when Cushing and his pupils made their far-reaching studies of the hypophysis and its neighborhood, that the notion of metabolic control by brain centers gained any real acceptance. The present-day concept of this influence of the central nervous system is given by Ranson⁴ as follows:

Resting on the optic tract lateral to the chiasm is a compact group of rather large cells, the supra-optic nuclei. Fibres arising in this nucleus along with some other fibres of hypothalamic origin run along the infundibulum to the posterior lobe of the hypophysis. Through this hypothalamo-hypophyseal tract the hypothalamus is in position to influence the functions of the hypophysis. One or the other of these two structures or both together exert an important control over the utilization of sugar, fat and water in the body.

To this Wiggers⁵ adds:

The structures of the hypothalamus are head centers for the sympathetic nervous system. Stimulation or lesions in this region may cause alterations in heart rate and blood pressure, sweat secretion, carbohydrate protein and fat metabolism, temperature regulation, evacuation of bladder and rectum, polyuria, dilatation of the pupils, widening of the palpebral fissures and bulging of the eyeballs.

Changes in body metabolism due to tumors involving this region are well recognized. Disorders following encephalitis of this area of the brain are not uncommon; comparable changes following trauma, however, are much less frequent, and it is with these disturbances of metabolism associated with head injuries that the present paper is concerned.

That such changes do occur has been noted by several writers. Bailev,⁶ in 1906, reported the appearance of transient glycosuria, lasting from twenty-four hours to five or six days, in patients with head injuries. This was found with fractures of the vault or of the base, and in some patients with no known fracture. In some cases the glycosuria was accompanied by an increase in the amount of urine, and in others polyuria existed without sugar. In 1940 Gross and Ehrlich⁷ mentioned glycosuria due to hypothalamic damage and stated that diabetes insipidus might arise from the same cause.⁸ Such injury was considered likelier to occur in the presence of fractures of the middle cranial fossa. Rowbotham,⁹ in 1942, gave the following interesting description:

Traumatic diabetes insipidus usually declares itself early in convalescence though it may not appear till several months after the injury. The outstanding symptom in this condition is insatiable thirst with a desire for water to assuage it. In severe cases a patient will drink 1 or 2 pints of water at a time and has to take copious supplies to bed with him as he so often awakens in the night and wants to drink. Fluids taken by mouth are rapidly excreted by the kidneys so that a patient tends to lose weight rather than to become waterlogged. Severe headaches, loss of physical energy, and mental depression are commonly associated with the symptoms of thirst. One young patient of mine who had been severely concussed and whose skull had been fractured through the pituitary fossa needed at least 12 pints of fluid in the day to satisfy his thirst, and once drank as many as 15 pints. The amount of water he passed was graphically described by his mother as being worthy of a donkey. In fact a large bucket was left under the bed for his use as his nocturnal peripatations used to disturb the whole household. This disturbance of

water metabolism was readily controlled by hypodermic injections of 0.5 cc. of pituitin night and morning. In six months after the injury this young man made a complete recovery. The tendency in all cases of traumatic diabetes insipidus is toward spontaneous cure. It is useless to restrict the amounts of fluids taken in an attempt to control the diabetes because this only leads to dehydration and toxemia. Usually injections of pituitin will keep a patient's thirst under reasonable control until spontaneous cure of the diabetes results. Severe and persistent cases may necessitate a total thyroidectomy as suggested by the work of Mahoney and Sheehan.

All these are cases of disturbed use of sugar and water in the body. The only example of upset fat metabolism of which I have found a report thus far is also given by Rowbotham.¹⁰

A pathological increase in weight due to excessive deposits of fat occasionally results from a basal injury, as evidenced by the case of a late Professor of Surgery in Manchester who fell from a horse and fractured the base of his skull. Following the injury, he became extremely stout, and this stoutness was associated with very definite dispositional changes.

The small number of reports of actual patients suffering from these disorders indicates either a lack of interest in these conditions or a considerable rarity of occurrence. My interest was aroused by the onset of severe diabetes insipidus in one patient and of an unusual disturbance of fat metabolism in another, in both, the findings were so striking that they demanded attention, stimulating a search for similar disorders in other patients. In the treatment of over 2500 patients with head injuries in the past ten years 7 cases of metabolic disturbance, 2 of sugar metabolism, 4 of water metabolism and 1 of fat metabolism have been noted, none involving protein metabolism have been recognized. It is not at all unlikely that many minor disorders have been overlooked, since interest was only recently directed to this subject. A careful study of these factors in all patients is now being made, in the hope that a reasonably accurate estimate of their incidence will be possible.

SUGAR METABOLISM

Only 1 case of transient glycosuria similar to that reported by Bailev⁶ has been observed. This occurred in a patient who later developed diabetes insipidus and whose record is more fully discussed in the consideration of water metabolism. Since many of the patients were given glucose by vein soon after the injury, some minor disturbances may well have been concealed. Another case of upset sugar metabolism was the following:

A 27-year-old man was admitted to the hospital on April 28, 1945 following an automobile accident in which he was said to have struck his head on some part of the car. On admission he was in severe traumatic shock and was in coma, with evidence of serious generalized brain damage but without clinical signs of skull fracture. It was learned that he was mildly diabetic and had been taking 20 units of protamine insulin daily. In view of this, the control of the diabetes was kept in mind from the start, and the Medical Service took over that part of the problem. There was no indication that the coma was in any way due to diabetes — the urine showed a +++ test for sugar and no acetone, and the blood

tomy been performed. In 1 case the operation was performed during the first trimester, so far as we know this is the first case on record treated in this manner. In the other cases the interval between operation and pregnancy ranged from three to ninety-six months, the average being thirty months.

CONCLUSIONS

It is known that lumbodorsal splanchnicectomy is a useful therapeutic measure in the treatment of hypertension and hypertensive cardiovascular disease.

Following a satisfactory response to operation, pregnancy, if carefully supervised, appears to be safe and permissible.

The experiences presented above lead us to believe that following this operation certain hypertensive women may be able to tolerate pregnancy, which

would otherwise be impossible or extremely hazardous. This is particularly true in the younger age group with severe essential and even malignant hypertension.

REFERENCES

- 1 Corwin, J., and Herrick, W. W. Toxemias of pregnancy in relation to chronic cardiovascular and renal disease. *Am J Obst & Gynec* 14: 783-796, 1927.
- 2 *Idem*. Relation of hypertensive toxemia of pregnancy to chronic cardiovascular disease. *J A M A* 88: 457-459, 1927.
- 3 Watson, B. P. Cited by Taussig, F. J. *Abortion, Spontaneous and Induced. Medical and social aspects*. 536 pp. St. Louis: C. V. Mosby Co., 1936.
- 4 Fishberg, A. M. *Hypertension and Nephritis*. Third edition. 668 pp. Philadelphia: Lea and Febiger, 1934.
- 5 Smithwick, R. H. Technique for splanchnic resection for hypertension. preliminary report. *Surgery* 71: 8, 1940.
- 6 *Idem*. Surgical treatment of hypertension. Effect of radical (lumbodorsal) splanchnicectomy on hypertensive state of 156 patients followed one to five years. *Arch Surg* 49: 180-193, 1944.
- 7 *Idem*. Surgical treatment of hypertension. Some circumstances under which lumbodorsal splanchnicectomy appears to be inadvisable in hypertensive patients. *New York State J Med* 44: 2693-2704, 1944.
- 8 Peet, M. M. Surgical treatment of hypertension. *J Internat de Chir* 5: 1-40, 1940.

DISTURBANCES OF METABOLISM ASSOCIATED WITH HEAD INJURIES*

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Diabetes is a wonderful affection, not very frequent among men, being a melting down of the flesh and limbs into urine. Its cause is of a cold and humid nature as in dropsy. The course is the common one, namely the kidneys and bladder, for the patients never stop making water, but the flow is incessant, as if from the opening of aqueducts. The nature of the disease, then, is chronic, and it takes a long period to form, but the patient is short-lived, if the constitution of the disease be completely established, for the melting is rapid, the death speedy. Moreover life is disgusting and painful, thirst, unquenchable, excessive drinking, which however, is disproportionate to the large quantity of urine, for more urine is passed, and one cannot stop them either from drinking or making water. Or if for a time they abstain from drinking, their mouth becomes parched and their body dry, the viscera seem as if scorched up, they are affected with nausea, restlessness, and a burning thirst, and at no distant time they expire. Thirst, as if scorched up with fire. But by what method could they be restrained from making water? Or how can shame become more potent than pain? and even if they were to restrain themselves for a short time, they become swelled in the loins, scrotum, and hips, and when they give vent, they discharge the collected urine, and the swellings subside, for the overflow passes to the bladder. Hence the disease appears to me to have got the name diabetes, as if from the Greek word *διαβητης* (which signifies a siphon), because the fluid does not remain in the body, but uses the man's body as a ladder (*διαβαλῶν*)‡ whereby to leave it. The cause of it may be that some of the acute diseases may have terminated in this, and during the crisis of the disease may have left some malignity lurking in the part. It is not improbable also, that something pernicious, derived from the other diseases

which attack the bladder and kidneys, may sometimes prove the cause of this affection.

THIS vivid description was written by Aretaeus, the Cappadocian,¹ who lived around 200 A.D. and whose careful accounts of pathologic conditions rank next to those of Hippocrates. It is interesting to note that this picture includes features of diabetes insipidus, diabetes mellitus and nephritis, this confusion persisted for many years. In the seventh century the Brahmin physician Susruta recognized the "honey urine," and four hundred years later Avicenna noted the sweet taste of the urine. It was not until the seventeenth century, however, that Thomas Willis made a clear distinction between diabetes mellitus and diabetes insipidus, followed in a few years by Johann Brunner's early experimental proof of the relation of the pancreas to diabetes mellitus. The relation of the brain to these processes was indicated by Claude Bernard's puncture of the fourth ventricle with resultant glycosuria in 1849. Bramwell,³ in 1888, stated as follows:

Tumours of the pituitary body are in many instances attended with an excessive development of the subcutaneous fat, and in some cases with the presence of sugar in the urine or with simple polyuria (diabetes insipidus). Whether these symptoms are due to the fact that the pituitary body is itself diseased, or whether, as seems more likely, to the secondary results which tumours in this situation produce in the surrounding cerebral tissue, has not yet been decided.

These investigators were apparently well ahead of their times, for it was not until early in the present

*Presented at the annual meeting of the New England Surgical Society, Worcester, October 4, 1946.

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‡This Greek word might be better translated literally "something to step through." The Latin translation is "quia humor in corpore non remanet, sed homine tanquam canali quodam, ad effluendum utitur" — that is "because the fluid does not remain in the body but uses the man as a sort of water pipe for flowing off."

of thyroid overactivity, but the basal metabolic rate was -24 per cent. This excess appetite has decreased, but 4 weeks ago he began to drink large amounts of water and other fluids, which failed to satisfy his thirst, and passed large quantities of urine. According to home records whose accuracy may be open to some question, the intake was from 5000 to 6000 cc., and the output 7000 to 8000 cc. Examination of the urine showed a specific gravity of 1.001, with no albumin or sugar and with no abnormal elements in the sediment. Examination of the blood showed normal values for urea nitrogen and sugar, with that for cholesterol slightly elevated to 252 mg per 100 cc. The patient has been treated with injections of Pituitrin, and a week ago the intake and output were approximately 2000 cc. each, and the specific gravity of the urine was 1.010. It seems not unlikely that he has metabolic disorders involving more than the use of water, and he is being studied with this possibility in mind.

FAT METABOLISM

The single case of disturbed fat metabolism after head injury was as follows

In February, 1945, a 47-year-old shipyard foreman entered the hospital about two weeks after a fall in which he had struck the back of the head. There had been a short period of unconsciousness followed by severe occipital headache and two episodes of vomiting. He then became lethargic and felt weak, was unable to concentrate and had partial amnesia for recent and remote events. Prior to the accident he had had charge of the work on three different ways at the yard, his duties involving constant climbing and physical activity, and he had lost no time from work. He had worked many hours overtime and felt somewhat tired, but his superiors considered his work excellent.

Physical examination showed a healed laceration about 5 cm. long, in the occipital region. The right pupil was slightly smaller than the left, both reacted sluggishly to light, the left a little more slowly than the right. The optic disks were normal, there was slight weakness of the right masseter muscle and of the right facial muscles, the superficial reflexes were diminished on the right and the deep reflexes were diminished on the left. X-ray films of the skull, including particular examination of the sella showed no fracture. Lumbar-puncture findings were within normal limits.

It was at first thought that the patient might have a subdural hematoma, but the symptoms improved so much on bed rest that exploration was considered inadvisable. In the course of a routine examination of the blood he was found to have a grossly visible lipemia, and studies to determine its cause were begun. The urine was normal except for a slight trace of protein and a few granular hyaline casts. Examination of the blood showed normal red-cell and white-cell counts and differential distribution and a normal amount of hemoglobin, the urea nitrogen, total protein and glucose levels were normal. The total fat in the blood was 5 per cent (normal, 0.5 to 0.7 per cent). The cholesterol was 584 mg per 100 cc. (high normal, 220 mg). The total blood lipid was 44 per cent, and the lipid phosphorus was 21.5 mg per 100 cc. The prothrombin time and icteric index were normal, and a glucose-tolerance test was also normal. A hippuric acid test was 145 per cent of normal. There was no evidence of tachyarrhythmias.

On repeated examinations the lipemia persisted and the cholesterol stayed at about the same level. After careful consideration, the Medical Service concluded that the patient had a lipemia of unknown origin. A well known authority on fat metabolism saw the patient and could give no explanation for the lipemia other than the trauma, he believed that if the disturbance in the use of fat disappeared as the head injury cleared it would confirm the impression that the condition was due to brain damage. The neurologic signs subsided slowly, and the patient was discharged at the end of 1 month complaining of occasional headaches, irritability, depression, muscular weakness and easy fatigability.

His condition has been followed since that time by clinical examinations and cholesterol determinations. In April, 1946, the cholesterol was 680 mg per 100 cc., in May it was 432 mg, and in July it was 496 mg. At that time the patient was

put on a diet low in cholesterol, and by October the cholesterol had dropped to 284 mg per 100 cc., he was much less irritable and was able to undertake some physical activity without marked fatigue. Eleven months after the accident the cholesterol was 176 mg per 100 cc. and the patient felt much better. With the withdrawal of most of the dietary restrictions the cholesterol rose to a little above normal levels, but it has now leveled off. The patient's strength is returning, his disposition is good and he is able to work.

In this case as in diabetes insipidus, it seems likely that treatment served to relieve symptoms by lowering the amount of cholesterol in the blood without actually affecting the course of the disease.

SUMMARY

Seven cases of metabolic disturbance associated with head injuries are presented for consideration. There is, of course, no real proof that any one of these examples of abnormal metabolism was actually due to a traumatic lesion of the hypothalamic region, no study was made prior to the injury, there was no death, and tissue examination was not possible. The patients represented a group of supposedly normal people who suffered head injuries involving slight to severe brain damage, who then, at periods varying from a few hours to three years later, developed disturbances in the use of sugar, water and fat such as those known to occur when the hypothalamus is injured, and whose disorders cleared up as the head injury healed. It thus seems reasonable to suppose that brain damage was a causal factor. A realization of the possible occurrence of such upsets, and a continued search for them will, in all probability, result in more frequent recognition and a better understanding of these interesting disturbances of metabolism.

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REFERENCES

- 1 *The Extent Works of Aretaeus the Cappadocian*, 510 pp. Translated and edited by F. Adams. London: Sydenham Society 1856. P. 338.
- 2 *Aretaeus Cappadocensis Opera Omnia*, 362 pp. Translated and edited by C. G. Kühn. Lipsiae 1828. P. 133.
- 3 Bramwell B. *Intracranial Tumours*, 270 pp. Edinburgh: J. J. Pentland, 1888. P. 164.
- 4 Ranson S. W. *The Anatomy of the Nervous System from the Standpoint of Development and Function*, Fifth edition, 501 pp. Philadelphia and London: W. B. Saunders Company 1936. P. 214.
- 5 Wiggers, C. J. *Physiology in Health and Disease*, 1156 pp. Philadelphia: Lea and Febiger 1934. P. 223.
- 6 Bailey P. *Diseases of the Nervous System Resulting from Accidents and Injury*, 627 pp. New York and London: D. Appleton & Company 1906. P. 61.
- 7 Gross S. W., and Ehrlich W. *Diagnosis and Treatment of Head Injuries*, 275 pp. New York and London: Paul B. Hoeber, Inc., 1940. P. 70.
- 8 *Ibid* P. 223.
- 9 Rowbotham G. W. *Acute Injuries of the Head: Their diagnosis, treatment, complications and sequelae*, 268 pp. Baltimore: William Wood and Company 1942. P. 211.
- 10 *Ibid* P. 212.
- 11 Cushing H. *Papers Relating to the Pustular Body, Hypothalamus and Parasympathetic Nervous System*, 234 pp. Springfield and Baltimore: Charles C. Thomas 1932. P. 35.

DISCUSSION

Dr. DONALD MURRO (Boston). This excellent and well documented paper deserves more than passing notice. The subject is extremely important and so far as I know, nothing so thorough as this has previously been published.

a study of this aspect of the epidemiology was instituted. Although influenza was prevalent throughout all schools in Needham, the study reported in this paper was limited to the high school, the junior high school and one of the elementary schools (Avery School).

With the co-operation of the local school and health-department nurses, visits were made between December 13 and 16 to the junior high school and to the homes of some of the pupils who were absent because of symptoms of influenza. At that time detailed histories were obtained, physical examinations were done on a number of the pupils who were acutely ill and blood was drawn for serologic studies. Throat garglings were also obtained from a few patients who were acutely ill with typical symptoms of clinical influenza and with temperatures of 101°F or higher. Histories concerning recent illness and blood for serologic studies were also obtained from as many household contacts as possible. A second visit was made to each of the same homes between December 29 and January 2, when second samples of blood were drawn and individual histories taken from the patients and the household contacts.

Epidemiologic data concerning illnesses and absenteeism during the period of the epidemic were obtained by means of a questionnaire given to each student in the three schools chosen for the study. Again, the school and local health-department nurses participated by explaining to teachers, parents and pupils the purpose of the investigation and by distributing and collecting the questionnaires. The school records were also examined for detailed information concerning absenteeism.

In an attempt to differentiate cases of common cold and other illness not related to influenza, specific information was sought in the questionnaire concerning such symptoms as malaise, headache, cough, coryza, sore throat, pain in the eyeballs, back and extremities, vomiting and diarrhea. There were other questions regarding date of onset, duration of symptoms, the presence or absence of fever and the total duration and degree of temperature rise. Patients presenting a majority of the symptoms mentioned above, in addition to a fever of at least twenty-four hours' duration, were tabulated as cases of influenza. Fortunately, the clinical picture was quite definite, the onset was sudden, prostration marked and in at least half the cases studied the duration of illness was four days or longer. The incidence of the common cold was low in this community during the time of the epidemic.

LABORATORY STUDIES

The methods used in the laboratory investigations and the results obtained are presented in detail elsewhere.¹¹ Attempts to isolate viruses from the throat washings of the patients from Needham were unsuccessful at first. Two strains of virus, however, were readily established in other cases that were

studied at that time, and a third strain was subsequently isolated in one of the Needham cases. These epidemic strains were identified as influenza B and were used for the serologic studies along with the PR8 strain of influenza A virus and the Lee strain of influenza B virus. Tests for inhibition of chicken erythrocyte agglutination and complement-fixation tests were done on serums taken from patients during the acute and convalescent phases and on those

TABLE 1 *Results of Tests for Influenza Antibodies in Cases and Household Contacts*

SUBJECTS	NO TESTED	NO SHOWING SIGNIFICANT RISE IN ANTIBODY TITERS	
		INFLUENZA A PR8 strain	INFLUENZA B Lee epidemic strains
Patients with clinical influenza	19	0	13*
Household contacts	20	0	0
With symptoms of common cold	4	0	0
With gastrointestinal symptoms	4	0	0
Without illness	12	0	0

*An additional case showed a rise by complement fixation but not by inhibition of agglutination.

obtained at the same time from the household contacts. The results of the serologic tests are summarized in Table 1.

Of the 19 typical cases of clinical influenza included in this study 16 yielded convincing evidence of infection with influenza B virus by significant, and in most cases marked, rises in the titers of antibodies for the Lee strain and for the epidemic strains but not for the PR8 strain. The 3 cases in which no rise in antibodies was demonstrated for any of the viruses used were all in members of the same family, and these were the only persons studied in that household.

All the household contacts who did not have symptoms of clinical influenza failed to show a significant — that is, a fourfold — rise in titer of antibodies for either the PR8 strain of influenza A virus or the Lee strain of influenza B virus. The serums of these persons were also tested with the epidemic strains, and no significant rise in titer of antibodies for any of them was demonstrated. Included among the contacts were 4 subjects who had coryza without fever or systemic symptoms and were regarded as having the common cold, 4 others who had low-grade fever and gastrointestinal symptoms, mostly diarrhea, and 12 healthy persons who had had no recent illness. Only 2 of the contacts were school children, the others were adults — most of them parents of the patients with influenza.

EPIDEMIOLOGY

During the interval December 2–21 a total of 484 cases of influenzalike infection occurred in the three schools included in the study. The attack rate was highest — 53.7 per cent — in the junior high school, and lowest — 24.4 per cent — in the senior high

The problem of the initiation of diabetes mellitus by trauma to the head is brought up from time to time before compensation boards in various states, and I happen to have been involved in such a discussion. On a search for authoritative statements regarding whether or not trauma to the head actually caused diabetes mellitus, it was impossible to find any really substantive statements. Now we have an authority that we can quote.

In connection with this experience, I called Dr. Elliott P. Joslin to find out whether he had any knowledge about the

causal relation between head injury and diabetes mellitus. He stated that, so far as he knew, there is no such relation. In my experience, I have not knowingly seen a patient who has sustained a head injury and who, as a result of that injury, has had diabetes mellitus. The combination is not frequent.

Diabetes insipidus, of course, is a different story, although a relatively rare disease, it is, again, extremely useful to have these cases on record, particularly when they have been worked up so carefully.

AN OUTBREAK OF INFLUENZA B INFECTION*

Epidemiologic Observations

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ALTHOUGH much knowledge concerning the epidemiology of influenza has been acquired over the years, more specific information has awaited the isolation of the etiologic agents. The discovery of the influenza B virus in 1940 simultaneously by Francis¹ and Magill² greatly facilitated the researches on the epidemiology of this disease. Nevertheless, data concerning the transmission of influenza B have not accumulated at a rapid rate. In some outbreaks it has been difficult or impossible to isolate the influenza B virus, and identification of cases in such circumstances necessarily depended on serologic studies. Furthermore, in extensive epidemics, it is not often practical to obtain acute and convalescent blood specimens from more than small samples of the population being investigated.

It has been shown that influenza B infection occurs as both an endemic and an epidemic disease. In Argentina, for example, sporadic cases of influenza B infection appeared in 1941 over a period of several months (June to October). This was in contrast to a sharp outbreak of influenza A infection during the previous year.³ Beveridge and Williams⁴ noted the sporadic occurrence of influenza B infection in Australia from June to September, 1943. Hare et al.⁵ reported a high incidence of upper respiratory infection in various localities in Canada. Serologic evidence indicated that 23 per cent of the cases were due to influenza B virus. Localized outbreaks, on

the other hand, have been reported from a convalescent home¹ and from a hospital for mental diseases. In the latter institution 71 patients out of 144 developed influenza B infection. In one unit the combined incidence of clinical and subclinical influenza was 20 per cent.

Influenza B may occur either alone or in association with influenza A. Lennette et al.,⁷ in a study of twelve outbreaks of influenza, found cases of influenza A infection in all but two epidemics, whereas cases of influenza B infection were encountered in only five epidemics. Influenza of unknown etiology occurred in each epidemic and accounted for 11 to 80 per cent of all the cases.

There is some statistical evidence that widespread epidemics of influenza B infection have occurred at intervals of four to six years.⁸ Francis⁹ suggested a four-year cycle on the basis of two known widespread epidemics of influenza B infection in 1936 and 1940.

Beginning in mid-April, 1945, small outbreaks of influenza B infection were reported from many areas in and outside the United States and were identified serologically or by virus isolation.¹⁰ Late in November and in December of that year an increased incidence of clinical influenza was noted in several communities in the Greater Boston area. Although the infection was generally prevalent throughout the entire area, there was considerable variation in incidence from one community to another.

PURPOSE AND METHODS

During the second week of December, 1945, our attention was called to reports indicating that influenza had assumed epidemic proportions in the schools of Needham, Massachusetts. In the junior high school, with an enrollment of 577 children, 50 per cent absenteeism had occurred. In the absence of detailed information in the literature concerning the transmission of influenza B infection in schools,

*Presented at the annual meeting of the American Public Health Association, Cleveland, November 12, 1946.

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sions during the peak of the epidemic less than a third of the children out of school were absent because of influenza.

In all three schools the proportion of total absenteeism due to influenza increased as the epidemic progressed. On December 4 the percentages for the Avery School and the senior high and junior high schools were 4.0, 10.7 and 37.5 respectively, and ten days later they had risen to 31.0, 37.4 and 73.0 in the same order. In general the figures for percentage absenteeism due to influenza were high in the junior high school, low in the Avery School and intermediate in the high school. No other contagious disease was prevalent in the three schools during the period of the study. Hysteria on the part of parents who did not permit their children to attend school lest they be exposed to the infection was responsible for a large proportion of absenteeism due to causes other than influenza.

DISCUSSION

It has been stated that the virus of influenza B spreads less rapidly than that of most A strains and that ordinarily it does not produce extensive outbreaks.¹² The high incidence of this infection in the Needham schools is evidence that it may at times resemble influenza A virus in its rate of transmission. Well defined epidemic curves were noted in the three schools selected for the study and also in the individual grades of the junior high school. High attack rates prevailed in individual classrooms and throughout the school system.

The incidence of infection in the junior high and Avery schools was significantly higher than that in

to infection was present in each. It may therefore be postulated that the variation in age distribution was the prime factor in the difference between rates.

TABLE 3 *Attack Rates by Classroom and Grade (Junior High School)*

GRADE	ROOM NO.	NO. OF PUPILS	NO. ILL	ATTACK RATE %
Seventh	1	26	10	38.5
	2	0	1	4
	3	26	10	38.5
	04	28	15	53.6
	204	25	21	84.0
	05	29	12	41.4
Totals		167	51	
Average				45.5
Eighth	00	4	14	41.2
	01	5	26	68.4
	04	6	14	38.0
	05	7	22	66.7
	10	15	15	42.0
	12	1	29	82.9
Totals		211	120	
Average				56.9
Ninth	00	9	25	59.0
	01	5	19	50.0
	07	41	22	53.7
	08	4	20	44.4
	09	26	25	69.4
Totals		122	101	
Average				54.7
Grand totals		599	310	
Grand average				53.7

in the senior high school on the one hand and those in the junior high and Avery schools on the other.

The high attack rates observed in the Needham schools have particular significance when consideration is given to the choice of groups best suited for

TABLE 4 *Absenteeism during Influenza Outbreak*

DATE	AVERY SCHOOL*		SENIOR HIGH SCHOOL†		JUNIOR HIGH SCHOOL‡	
	TOTAL PUPILS ABSENT	PUPILS WITH INFLUENZA	TOTAL PUPILS ABSENT	PUPILS WITH INFLUENZA	TOTAL PUPILS ABSENT	PUPILS WITH INFLUENZA
December 1945						
3	31	1 (3.2%)	20	2 (10.0%)	25	5 (20.0%)
4	25	1 (4.0%)	28	5 (10.7%)	24	9 (37.5%)
5	26	2 (7.7%)	21	5 (16.1%)	25	8 (32.0%)
6	42	4 (9.5%)	36	7 (19.4%)	20	13 (45.3%)
7	63	5 (7.9%)	52	6 (11.5%)	50	27 (34.0%)
8	31	8 (25.8%)	54	8 (14.8%)	157	123 (78.3%)
9	35	12 (34.3%)	54	23 (42.6%)	189	135 (71.4%)
10	48	15 (31.2%)	66	29 (43.9%)	224	154 (68.8%)
11	50	15 (30.0%)	66	35 (50.0%)	238	188 (78.9%)
12	58	18 (31.0%)	91	34 (37.4%)	278	203 (73.0%)
13	104	31 (29.8%)	101	55 (54.5%)	216	181 (83.8%)
14	105	40 (38.8%)	120	62 (51.7%)	186	146 (78.5%)
15	98	38 (38.7%)	135	71 (52.6%)	175	129 (73.7%)
16	—	—	108	73 (24.7%)	340	129 (37.9%)
17	—	—	171	60 (35.1%)	197	102 (52.3%)
20	102	25 (24.5%)				

*Total school population 122

†Total school population 492.

‡Total school population 577

§Snowstorm occurred on this day

the senior high school. Both the senior and junior high schools were attended by pupils living throughout the entire community, and since cases were reported from every homeroom and grade in both schools, it is apparent that opportunity for exposure

to vaccination against influenza. It is apparent that in a susceptible population, large numbers of children will develop influenza B infection following adequate exposure and that an effective immunizing agent would be of value in diminishing school absenteeism.

school, the difference being significant statistically. The standard deviation of the difference between these rates is 29.3 ± 2.8 . The difference in the rates between the junior high and Avery schools, however, was not found to be statistically significant. The

forty-eight hours (Fig 2), indicating widespread dissemination of infection through all three grades at about the same time. Of 120 cases in the eighth grade 81, or 67 per cent, appeared in the seven-day period from December 7 to 13. In the ninth grade 64 of 109 patients, or 59 per cent, became ill during the same week. Although there was considerable variation in the curve for each grade, it is apparent that a fairly well defined rise and fall occurred in each group.

The attack rates in individual classrooms varied from 38.5 to 82.9 per cent. Out of seventeen classrooms in the junior high school, the attack rate was

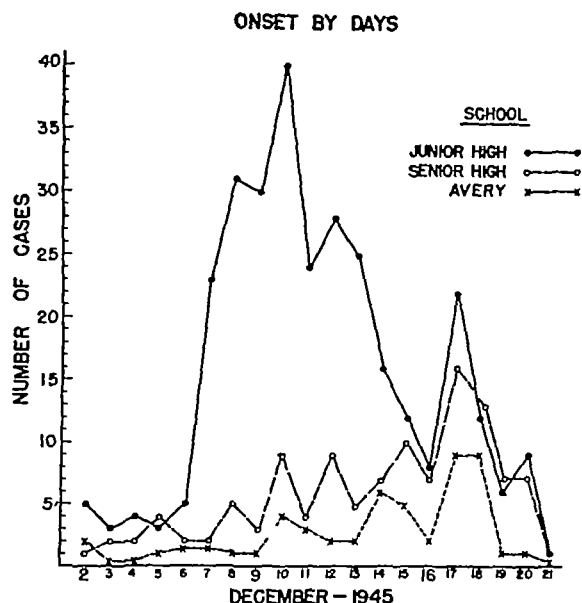


FIGURE 1 Distribution of Cases in All Schools according to Date of Onset

standard deviation of the difference between the latter rates is 9.2 ± 5.0 (Table 2).

The distribution of cases in the three schools according to the date of onset is presented in Figure 1.

TABLE 2 Attack Rates in Three Schools

SCHOOL	SCHOOL POPULATION	NO. OF CASES	ATTACK RATE %
Senior High	492	120	24.4 ± 1.94
Junior High	577	310	53.7 ± 2.08
Avery	122	54	44.7 ± 4.50
Totals	1191	484	
Average			40.6 ± 1.42

The day of highest incidence in the junior high school preceded that in the senior high and Avery schools by a week. A second peak occurred in the junior high school at the time of highest incidence in the other two. All peaks occurred at or just after a week end. A sharp epidemic curve was noted in all three schools.

The peak in the seventh, eighth and ninth grades of the junior high school occurred within a period of

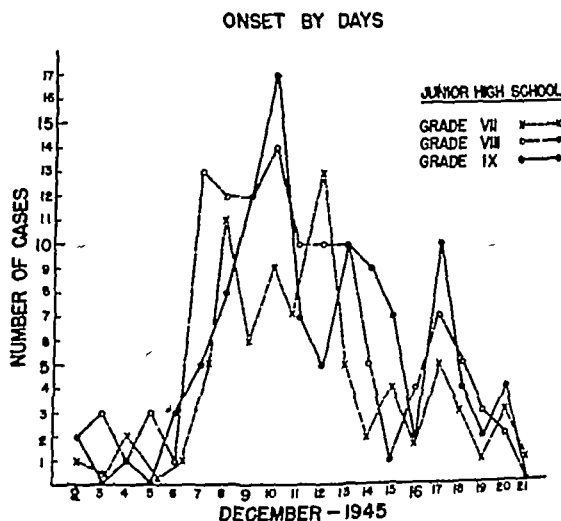


FIGURE 2 Distribution of Cases in the Junior High School according to Date of Onset

50 per cent or higher in nine and less than 40 per cent in three (Table 3). The attack rate for the entire school was 53.7 per cent, 310 children out of the total of 577 enrolled having developed clinical influenza from December 2 to 21.

Total absenteeism as compared with that caused by influenza is demonstrated in Table 4. In the junior high school at the height of the epidemic a major proportion of children absent from school were ill with influenza. On December 10, for example, 123 (78.3 per cent) of 157 absentees were ill with influenza and only 34 pupils (approximately 6 per cent) of the total enrolled were absent for causes other than influenza.

In the senior high school, where the attack rate was lower, the proportion of children absent because of influenza was considerably less than that in the junior high school. From December 10 to 18, at the very height of the epidemic, the percentage of absenteeism due to influenza varied from 14.8 to 54.5.

In the Avery School the bulk of absenteeism was due to causes other than influenza. On several occa-

- 9 Francis T., Jr. Factors conditioning resistance to epidemic influenza *The Beryll Journal* 37 69-99 1941-1942
- 10 Francis T., Jr., Salk, J. E., Jonas E. and Brace W. M. Protective effect of vaccination against epidemic influenza B *J. A. M. A.* 131 275-278 1946
- 11 Field, L. M., Barnes M. W., Meads M., Orr E. M. and Rubenstein, A. D. Influenza B in Needham, Massachusetts December 1945: serologic studies in cases and in family contacts *J. Lab. & Clin. Med.* 32 367-378 1947
- 12 Burnet F. M. Influenza and other respiratory infections *M. J. Australia* 2 16 1944
- 13 Stuart Harris C. H. et al. *A Study of Epidemic Influenza With special reference to the 1926-1927 epidemic* Medical Research Council Special Report Series No. 228 151 pp London His Majesty's Stationery Office 1928
- 14 Francis T. Jr., Pearson H. E., Salk J. E. and Brown P. N. Immunity in human subjects artificially infected with influenza virus Type B *Am. J. Pub. Health* 34 317-334 1944

MEDICAL PROGRESS

PEDIATRICS*

MEMBERS OF THE STAFFS OF THE CHILDREN'S AND INFANTS' HOSPITALS†

BOSTON

THE justification for considering pediatrics a specialty does not arise from its concern with a particular type of disease or with the special techniques necessary to deal with a particular region of the body, but rather from the nature of its patients, who are distinguished by an outstanding characteristic—they are constantly growing. The aim of the pediatrician is to assist, to the limit of his abilities, this process of growth so that his patient may increase "in wisdom and in stature." Thus, the basic goal of pediatrics is preventive, although it is concerned with curative medicine and surgery, and its scope naturally extends from the time of conception until the cessation of physical growth. This broad view has added to the concerns of the pediatrician the antenatal period on the one hand, when he must work with the obstetrician, and the period of adolescence on the other, when his interests begin to merge with those of the internist and gynecologist.

By the application of knowledge in the fields of nutrition and infectious disease, pediatricians and public-health workers have been remarkably successful in assisting the physical growth of children. This success only emphasizes their obvious failures. Accidents, particularly those due to automobiles, are the major cause of death in childhood, and yet physicians and public-health workers have given their prevention little thought. It is in the guidance of mental and emotional development that the shortcomings of present knowledge and practice are most apparent. The ultimate standard by which the success or failure of pediatrics must be judged is the extent to which its charges become well integrated, responsible citizens when they graduate to adult life. The prevalence of psychoneurotic disorders as a cause of rejection in Selective Service examinations and of disability in American troops has clearly indicated deficiencies in the field of

mental hygiene.¹ Success in this field will depend, as it does in that of physical hygiene, on a basic understanding of the normal pattern of growth and development.²

Although the care of both healthy and sick human beings in the growth period has become the special concern of pediatrics, it is doubtful whether there are sufficient pediatricians to provide for more than a fraction of the child population. The extent to which present facilities for the medical care of children are adequate and to which services to children are provided by pediatricians, by general practitioners or by other types of professional workers will be known when the present study of child health services³ is completed. This study, organized by the American Academy of Pediatrics, with the co-operation of the Children's Bureau and the United States Public Health Service, represents a laudable attempt by a voluntary medical organization to obtain the necessary information on which to base future plans for the improvement of medical care.

It is debatable whether the attempt should be made to provide pediatricians for all children. In society the unit is not the child but the family, all of whose members are involved whenever illness strikes anyone in the group. It is interesting to compare the emphasis on specialization in this country to the policy in Great Britain, where, traditionally, the pediatricians have been a small group of consultants, routine child care being given on the preventive side by public-health workers and on the curative side by general practitioners. In a recent report, the Pediatric Committee of the Royal College of Physicians of London⁴ states

The present policy of having two groups of medical personnel, the one engaged in preventive and the other in curative work, is good neither for the child nor the doctor. A long-term policy should aim at making the general practitioner primarily responsible for the medical care of the child, in both the prevention and treatment of disease, since he is the one best fitted to give this service in the home.

Ultimately, the normal channel through which the family seeks medical advice in health as well as the sickness should be by consultation with the family general practitioner.

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The data presented above offer some evidence of the reliability of absenteeism reports as an indication of the prevalence of influenza. Whatever the reason for the observed differences in the percentage of absenteeism due to influenza among the three schools, it appears that total absenteeism is sometimes a poor index of the prevalence of influenza.

Some information concerning the occurrence of subclinical infection with influenza B virus has been acquired from previous studies. Stuart-Harris et al.¹³ reported the cases of several patients who developed neutralizing antibodies following exposure to influenza B infection and remained symptom free. In 1944 Francis¹⁴ reported that 11 of 30 uninoculated controls without recognizable illness developed a significant rise in antibody level after a period of 14 days.¹⁴ During the course of an epidemic of influenza B infection in a mental institution, Nigg and her associates⁶ found that 14 per cent of blood specimens taken from 77 contacts who had not been ill showed positive complement-fixation reactions for influenza B virus in a dilution greater than 1:5.

In the present study significant rises in antibody titers for the influenza B viruses were demonstrated only in the blood of persons who had characteristic symptoms of infection. Identical results in this respect were shown in most cases both by the complement-fixation reaction and by tests for inhibition of chicken red-cell agglutination.

The apparent disparity between this and the previous studies noted above may have been a matter of strain peculiarity. It must be recalled, however, that the sample studied was small and that virus isolation was not attempted on healthy contacts. At any rate, significant antibody responses were demonstrated only in patients with clinical evidence of infection, and the existence of healthy carriers could not be postulated on the basis of serologic evidence alone.

It is noteworthy that of 19 persons considered to be ill with influenza, laboratory studies confirmed the clinical diagnosis in 16. In only 3 cases, all of which occurred in one family, did serologic tests fail to tally with the clinical impression. Although serologic studies were performed on a relatively small number of patients, it is reassuring that confirmation of the clinical diagnosis was obtained in a high proportion (84 per cent) of the cases studied in the laboratory. The uniform clinical picture manifested by the majority of patients and the sharp epidemic curve observed in the three schools and in the individual grades of the junior high school are further evidence that a single etiologic agent was responsible for this outbreak.

SUMMARY

During the course of an epidemic of influenza B infection reported in 1945 from many areas in and outside the United States, a sharp outbreak occurred in Needham, Massachusetts. An epidemiologic

and laboratory investigation was carried out in an elementary school and in the junior and senior high schools.

From December 2 to 21 a total of 484 cases of influenza occurred in the three schools, the attack rate per 100 pupils being 53.7 in the junior high, 44 in the elementary school and 24.4 in the senior high school. The distribution of cases by day of onset indicated a sharp epidemic curve in each of the three schools and in the individual grades of the junior high school. The day of highest incidence in the junior high school preceded that in the senior high and Avery schools by a week.

The attack rates in individual classrooms in the junior high school varied from 38.5 to 82.9 per cent. In seventeen classrooms in the junior high school the attack rate was 50 per cent or higher in nine and less than 40 per cent in only three.

Comparison of total absenteeism with that due to influenza during the course of the outbreak revealed marked differences among the three schools. In the junior high school, where the attack rate was highest, influenza was responsible for the greater part of the total school absenteeism. In the remaining two schools many children absent from school did not have influenza. The reliability of absenteeism as an index of the incidence of influenza is at times open to question.

Two strains of virus were readily isolated from cases in Boston, and a third strain was isolated from one of the Needham cases. These three epidemic strains were identified as influenza B viruses.

Of 19 typical cases of clinical influenza in Needham, serologic evidence of influenza B infection was obtained in 16. All asymptomatic contacts failed to show a rise in titer of antibodies for the influenza A and B viruses.

The confirmatory laboratory evidence, the uniform clinical picture manifested by the majority of patients and the sharp epidemic curves noted in all three schools suggest that a single etiologic agent was responsible for this outbreak.

We are indebted to the following officials of Needham for their assistance and for making this study possible: Berwood A. Newman, Superintendent of Schools, Robert McClellan, Health Officer, Rose M. Mayers, R.N., Board of Health Nurse, and Marion Maxwell, R.N. School Nurse.

REFERENCES

1. Francis, T., Jr. New type of virus from epidemic influenza. *Science* 92:405-408, 1940.
2. Magill, T. P. Virus from cases of influenza like upper respiratory infection. *Proc. Soc. Exper. Biol. & Med.* 45:162-164, 1940.
3. Taylor, R. M., Parodi, A. S., Fernandez, R. B., and Chialvo, R. J. Un estudio sobre la etiología de la influenza ocurrida en la Argentina durante 1941: comparación de la epidemiología de influenza A y B. *Rev. d'Inst. Biot. Buenos Aires* 11:44-57, 1942.
4. Beveridge, W. I. B., and Williams, S. E. Sporadic occurrence of influenza in Victoria during 1943. *M. J. Australia* 2:77-80, 1944.
5. Hare, R., Stamatic, D. M., and Jackson, J. Influenza amongst immunized and unimmunized population in 1943. *Canada J. Pub. Health* 34:442-452, 1943.
6. Nigg, C., Eklund, C. M., Wilson, D. E., and Crowley, J. H. Study of epidemic of influenza B. *Am. J. Hyg.* 35:265-284, 1942.
7. Lennette, E. H., Rickard, E. R., Hirst, G. F., and Horsfall, F. L., Jr. Diverse etiology of epidemic influenza. *Pub. Health Rep.* 56:1777-1788, 1941.
8. The Commission on Acute Respiratory Diseases, Fort Bragg, North Carolina. Periodicity of influenza. *Am. J. Hyg.* 4:29-37, 1946.

children a year rose in 1945 to 48. The mothers of 34 of these children gave a history of rubella in pregnancy.²¹ Seventeen per cent of the deaf children in this school had murmurs suggesting congenital heart lesions. Swan and Tostevin²² recently added 40 more cases of rubella during pregnancy to the two earlier series already studied by them. Of these 40 pregnancies, 37 resulted in malformed infants. In the same communication the authors reviewed 16 other pregnancies marked by measles, mumps, rubeola, herpes zoster or scarlet fever. In contrast to the overwhelming evidence of a relation between rubella and malformations, pregnancies associated with the other infections resulted somewhat equivocally. The numerical factors are, of course, such as to make the data on so few cases of limited value. Swan and Tostevin have made the reassuring observations that pregnancies beginning as early as two weeks after maternal rubella are apparently without fetal danger, and that those subsequent to the one complicated by rubella will also result in normal infants.

Among several American reports new and useful approaches to the problem have begun to appear. Cordes and Barber²³ describe the retarded lens development and differentiation of the eye of an embryo removed at the seventh or eighth week from a woman who had rubella a week before artificial termination of pregnancy. Fox and Bortin²⁴ and Aycock and Ingalls²⁵ have begun the essential task of tracing every infant whose mother is known to have had rubella during pregnancy. Their combined results, summarized in the most helpful review by the latter authors,²⁵ give a total of 11 women who developed German measles during the critical first trimester of pregnancy. Eight of the resultant infants were normal, whereas the other 3 were malformed, although in no case did the anomaly affect the eyes or the heart. This group, indicating a hazard of about 25 per cent to the fetus, is too small to allow more than the implication that the fetus can escape involvement.

Several agencies, among them the Massachusetts Department of Public Health²⁷ and a committee representing various national pediatric societies, with Dr. Herbert Miller as chairman, have begun studies by questionnaire to reach a more definite answer to the problem. Co-operation, which of course includes reporting of negative as well as positive results, is strongly urged on all physicians of whom inquiries will be made. Obviously, to know the fetal outcome in a large group of pregnancies associated with definite rubella will be of much greater value than knowledge of how many mothers of malformed infants had rubella during pregnancy. Under present knowledge and until such data are available, a physician whose patient develops definite rubella during the first trimester of pregnancy is forced to consider most seriously the artificial termination of the pregnancy. There are

as yet insufficient data to suggest a like procedure when other infectious diseases occur in early pregnancy.

PREVENTION OF INFECTIOUS DISEASE

Desirability of Exposure to Certain Contagious Diseases in Childhood

During the past few years the philosophy toward the common contagious diseases has markedly changed. Formerly, the appearance of cases of any of the communicable diseases in a group of children resulted in the application of strict quarantine measures to all the contacts. In actual practice such rigid quarantine was rarely successful in localizing an outbreak, but there are stronger reasons for a change in the practice. In the first place, the only protection against these illnesses, which practically everyone must have once in his lifetime, is the immunity that develops as a result of an attack. Secondly, these ailments, like most other infectious diseases, are apt to be much milder in childhood and increasingly serious as the age of the victim increases. Thirdly, the time lost from productive occupation is shorter in childhood and can be better spared. Finally, if the diseases are allowed to remain endemic in the community, devastating and widespread epidemics are prevented.

German measles and mumps provide the strongest argument in favor of childhood exposure. The severity of mumps in adult life, with the frequency of involvement of the gonads, pancreas and central nervous system, is much greater than that in childhood. Although sterility results from bilateral involvement of the testes in the male less often than is customarily supposed,²⁸ it may occur. Both diseases, notably rubella, have been incriminated as a cause of congenital defects in babies born to mothers who escaped the infections in childhood, only to develop them during the first trimester of pregnancy.¹⁵⁻²⁷

Thus, rather than attempt to prevent the spread of chicken pox, measles, German measles and mumps, physicians should encourage them to spread among healthy children. On the other hand, the physician must make it his responsibility to protect patients in whom one of these diseases might have serious consequences. This includes sick or debilitated children, pregnant women, susceptible men who for business reasons cannot afford to be ill and children under three years of age, in whom these diseases may be serious. The importance of assuming this responsibility if one adopts a *laissez faire* attitude in dealing with communicable disease in children is illustrated by a recently reported experience.²⁹ In a private school with an outbreak of mumps it was decided to allow the epidemic to run its course rather than to quarantine all susceptible contacts of the first case. The disease spread as anticipated among the children,

Consequently, the skill in pediatrics of the general practitioner must be adequate so he can play this essential role in child health particularly in the home

This review is written primarily for those general practitioners whose all-important work includes the care of infants and children. We have chosen to stress the preventive side of pediatrics because it occupies such a large part of the efforts of physicians engaged in pediatric practice. Certain fields, in which recent advances have been little short of miraculous, such as the surgical correction of congenital anomalies of the gastrointestinal tract or cardiovascular system, should be mentioned, but have merited separate reports.⁶⁻⁸ The availability of methods for the repair of these congenital defects places an additional burden of responsibility on the general practitioner for their early recognition. Of even greater interest is the accumulation of knowledge concerning the pathogenesis of these defects, since it points the way toward their prevention. This will be apparent in the following sections.

PRENATAL PEDIATRICS

Information related to the nonhereditary processes affecting the child in utero is still largely in the speculative stage. Exact details have not been explored, except in the matter of maternal and fetal blood incompatibilities, which will be the subject of another report.⁹ Progress in a few other matters of prenatal influence is briefly discussed below.

It has been clearly shown by Miller et al.¹⁰⁻¹² and by others¹³ that the infants of women who are, or who later become, diabetic present a collection of anatomic peculiarities acquired before birth. In association with these abnormalities the fetal and neonatal mortality is about 20 per cent, or six times the expected rate for normal pregnancies. This mortality is no less in pregnancies five years before the onset of the mother's diabetes than it is once diabetes has made its clinical appearance. Even ten to twenty years before this event, the fetal and neonatal loss is about three times that expected in women who do not later become diabetic. The fetuses and infants show one or several of the following characteristics: increased birth weight, cardiac enlargement, extramedullary hematopoiesis, hyperplasia of pancreatic islets and a tendency toward gross, nonspecific congenital anomalies.

A connection between this perversion of prenatal development and actual or potential maternal diabetes is obviously present, but its mechanism is completely unknown. Certainly, it has nothing to do with maternal hyperglycemia. Miller¹² lists certain reasons suggesting that the primary derangement is one of maternal anterior pituitary secretion. Whatever the explanation, it is apparent that normal women giving birth to infants weighing 9 pounds or more, or to those with unexplained cardiac hypertrophy or with unexplained features suggesting erythroblastosis, should be followed for

the later development of diabetes mellitus. Finally, of course, the live-born infant with any of these features should be watched with extraordinary care, since only symptomatic means are available for meeting a definite threat to survival.

The relation of maternal nutrition to the proper development and growth of the fetus has been demonstrated by numerous animal and human studies. Warkany's¹⁴ excellent review of these contributions — many of them his own — leaves little doubt that maldevelopment of the animal fetus may be thus brought about. Whether a large number of human congenital abnormalities have this factor as their basis is a problem not yet solved. Warkany's own experimental production of ocular maldevelopment by a maternal diet sharply limited in vitamin A has been confirmed locally in the past year.¹⁵ Food conditions associated with the recent war might be expected to produce deflection of human fetal growth and development. Butler and his associates¹¹ were unable to demonstrate any harm to infants born to ill nourished women who had been interned by the Japanese in the Philippines, but the number of their cases was relatively small. A larger group was studied in Holland, where marked general undernutrition of the urban populace occurred during the winter of 1944-1945.¹⁷ A significant increase in the frequency of congenital malformations was not discovered, although the deprivation was stringent enough to reduce the birth weights and birth lengths of infants born during the hunger months. A most striking feature of the Dutch situation was the development of amenorrhea in at least 50 per cent of women, so that the birth rate at corresponding later dates fell to below half the normal. The sharp decrease in births interfered with statistical evaluation of the importance of the small increase in malformations discovered. Perhaps, as Warkany¹⁴ has said, "the most serious malformation that can befall an infant may be never to be conceived at all."

Although the prenatal influence of maternal diet on fetal growth is an actuality, rather delicately balanced circumstances may be necessary for the potential deflection of fetal development in human subjects. Maternal diets both sufficient to allow conception and deficient enough to interfere with fetal development must fall in a rather narrow band of the nutritional spectrum. Long-continued depletion of the mother, as by improper nutrition for months or years before pregnancy, is likelier to be required than dietary deficiency merely during the pregnancy.

Interest and data concerning maternal infection during pregnancy as a cause of ocular, cardiac, auditory, cerebral and dental maldevelopments are accumulating.¹⁸⁻²³ Reports continue to appear from Australia concerning the effects of maternal rubella in the early part of pregnancy.²⁴⁻²⁶ At a school for the deaf in Brisbane the average admission rate of 7

Immunization of children against both diphtheria and tetanus can be carried out with combined toxoid with good results and few reactions.³⁵ Adolescents and adults are much less liable to severe reactions to tetanus than to diphtheria toxoid, which is fortunate since the immunized person should receive a booster dose of 0.5 to 1.0 cc of tetanus toxoid if he sustains a severe injury that is likely to lead to tetanus. Primary immunization with combined toxoid should be given at the age of six months. Fluid toxoid requires three doses spaced at intervals of two to four weeks, and alum-precipitated toxoid two doses spaced at an interval of two to four months. A disadvantage of the latter is the occasional development of sterile abscesses and the somewhat greater frequency of sensitization to certain components of the toxoid due to the marked adjuvant effect of alum on sensitization. A booster dose of 0.5 cc of the combined toxoids should certainly be given at the age of five years when school starts and perhaps at two years as well, owing to the increased prevalence of diphtheria.^{30, 36}

Vaccination against pertussis is effective in diminishing the incidence and severity of the disease provided an adequate dose of properly prepared Phase I vaccine is used.³⁷ If reactions to pertussis vaccine were not relatively frequent and occasionally severe, there would be no hesitation in recommending its universal administration in infancy. The hazard of the disease is principally in the first year of life, and if, as Sauer³⁸ maintains, immunization should not be started before the age of six months, immunity will not be established until the age of nine or ten months. Recent studies, however, suggest that early immunization can establish adequate antibody levels if alum-precipitated vaccine is used.^{39, 40} If infants are kept at home during the first year, they will not often be exposed without the knowledge of the parents or physician. The administration of hyperimmune human serum,⁴¹ hyperimmune rabbit serum⁴² or concentrated human hyperimmune globulin⁴³ in adequate doses to exposed infants should give passive protection and will usually ameliorate the disease if it develops.⁴⁴ The introduction of streptomycin affords another potential method of treating the disease. In view of all these facts, the use of pertussis vaccine as a routine procedure is somewhat less urgent than formerly but should be encouraged whenever there is a real risk of exposure, particularly in infants in families with a number of older children in school, since pertussis is a serious disease in infancy. In children who have been immunized to pertussis and who are exposed to the disease after six months or more a booster dose of 1.0 cc subcutaneously is recommended. With the general use of pertussis immunization, school quarantine measures should be eliminated,*

since many immunized children escape infection or have unrecognized mild attacks of the disease.

There has been a steady increase in the practice of using combined antigens for routine inoculations.⁴⁵ Combined diphtheria and tetanus toxoid has much to recommend it. Combinations of these two toxoids with pertussis vaccine, either in a fluid state or absorbed on aluminum hydroxide, are available. The advantage of these triple combinations lies in the reduction of the number of injections. When alum precipitation was used with pertussis vaccine, the reaction rate appeared to be increased, but there is insufficient published evidence for an evaluation of the newer aluminum hydroxide preparations.⁴⁶ One reason to question the general use of these triple combined vaccines is psychologic. Immunization with the two toxoids is essential. Reactions are chiefly due to the pertussis vaccine, and with triple vaccines, the occurrence of severe reactions may discourage completion of the course of immunization and discredit the diphtheria toxoid that every child must have.

There are no other vaccines that should be given serious consideration for routine use in children in New England. Influenza A and B vaccine has been proved to diminish the attack rate of epidemic influenza in outbreaks due to both A and B types of virus.^{47, 48} Its use in children, however, seems hardly worth while. Influenza, like other infectious diseases, is milder in childhood than in adult life. Since the duration of immunity from vaccination is probably short, reactions to the various types of vaccines are often considerable and the development of hypersensitivity to egg protein is a possibility, there is something to be said for permitting children to acquire a basic immunity by natural infection with the virus, which may afford some degree of protection to the inevitable exposures in later life.

Scarlet-fever immunization has enjoyed a varying vogue. Since protection is produced only against the toxin and not against infection with the hemolytic streptococcus its value to the child is open to question. Moreover, reactions with the standard plan of toxin injections are often considerable and even dangerous. Since severe, toxic scarlet fever rarely occurs today and penicillin therapy adequately controls the septic aspects of streptococcal infection, there is little justification for immunization at present. The intradermal injection of a tannic acid precipitated toxin may obviate some of the objections to scarlet-fever immunization.⁴⁹

The question of immunization against typhoid fever, typhus, cholera, plague and yellow fever may arise in children going overseas to join their families in Europe and Asia. It should be emphasized that, with these diseases, immunization is only one of the important measures necessary to prevent the infection. Since the food of the infant can be sterilized by an intelligent mother, there appears to be little need for cholera or typhoid injections before six

*Families, however, should be notified of the presence of pertussis or other contagious diseases in the school so as to permit the protection of vulnerable persons, such as newborn babies by isolation or passive immunization.

but unfortunately a number of cases of severe mumps, including several of orchitis and meningo-encephalitis, resulted when the virus was carried to nonimmune parents by the children. It should also be stressed that, although quarantine of contacts is not recommended in the group of diseases mentioned, such an attitude cannot be adopted with diphtheria because of its serious consequences.

Immunization

The efficacy of active immunization has been conclusively demonstrated in diphtheria, tetanus and smallpox. Vaccination methods have also been developed for a number of other diseases, against which active immunization appears to have a definite but less clear-cut effect. In many cases—for example typhoid fever and typhus—it is difficult to apportion the credit for control of epidemics between immunization and effective sanitation.

Routine immunization is the responsibility of every physician who takes care of children. A recent progress report³⁰ presented an exhaustive review of the field of active immunization, so that this report is confined to an attempt to answer the following practical questions:

- Against what diseases should children in New England be immunized?
- When should immunization be carried out?
- What types of preparation should be used?
- How often should reinoculation be performed?
- What dangers are there in immunization?

Our attempt to answer these questions may appear dogmatic. This is not the intention. There are a number of methods for achieving the same objective, and the factors in each case should be weighed. For example, smallpox vaccination should be the initial immunization procedure in any community where the disease has recently been reported, whereas it can ordinarily be deferred until tetanus inoculations have been given. The essence of good medical practice is flexibility based on an understanding of basic principles.

Vaccination against smallpox is absolutely essential. Cases of the disease continue to occur in the United States, and the freedom from epidemics is mainly due to nearly universal vaccination. It should be performed in the first year, since the incidence of its chief complication, postvaccinal encephalitis, is considerably higher in persons whose initial vaccination is performed in childhood or adult life.³¹ Since tetanus has followed vaccination, particularly when tight shields were used,³² vaccination after the completion of tetanus immunization is sometimes preferred. The principal causes of failure to obtain a reaction is a lack of appreciation that the vaccine is a living virus, which may be inactivated by improper or prolonged storage or by

the use of alcohol, iodine or mercurial antiseptics to cleanse the skin. Only a volatile substance such as ether or acetone should be used, and this should be allowed to evaporate before the skin is pricked. All the lymph in the tube should be squeezed on the skin, because the lymph may separate from the glycerin. Revaccination should be carried out routinely when the child first goes to school, again at the age of eighteen and when there is an outbreak of the disease or the person is going to a foreign country. In revaccination the physician should not be satisfied with a negative reaction but should insist on an immune, modified or typical response.

Diphtheria is one of the most serious preventable health hazards to children in New England, and hence immunization should be given as early as practicable. The original idea that one could not obtain a satisfactory immunity by inoculations given to infants under six months of age is now undergoing close scrutiny, but it is too early to recommend change of the standard procedure of beginning diphtheria immunization at the age of six months. Formerly, most newborn infants were found to be Schick negative as a result of the passive transfer of maternal antitoxin. Now, however, there is a considerable percentage of Schick-positive persons in the adult population, and their infants will be born without such an immunity. This raises the question of early immunization of the infant or of prenatal immunization of the mother.³³ Unfortunately, adults frequently have severe local and constitutional reactions to diphtheria toxoid, so that immunization of the mother should not be considered until the latter half of pregnancy, when damage to the fetus by a reaction is no longer a real possibility. Until a more satisfactory method for immunization of adults against diphtheria is worked out, physicians should probably adopt the attitude of being alert to diagnose diphtheria infection and of beginning immunization promptly at the age of five or six months. If an infant is exposed to diphtheria, antitoxin should not be given unless clinical diphtheria develops. The choice of agents and times for booster doses of diphtheria toxoid is discussed below under tetanus immunization.

Tetanus immunization should be a routine procedure in childhood for the following reasons: it is an infrequent but dangerous disease, although it rarely occurs in adults except after serious injuries; a large proportion of cases in childhood follow injuries and infections so mild that the patients are unlikely to seek medical advice³⁴; the use of tetanus antitoxin may sensitize the patient to horse serum, making it difficult to administer diphtheria antitoxin subsequently, and if the patient has been immunized against tetanus, the physician is spared the frequently difficult decision regarding the advisability of administering tetanus antitoxin for many of the minor cuts and injuries in childhood.

bacterial respiratory infections. It is possible to diminish the bacterial content of air by the use of ultraviolet irradiation,⁶² by the vaporization of glycols⁶³ and by treating floors and bedding with oil to make bacteria and dust adhere.⁶⁴ Nevertheless, the rigid observance of strict isolation technic is an absolute necessity in the care of sick infants in a hospital, if the number of cross infections is to be reduced. Children with diarrhea, draining ears, acute respiratory infections and skin infections (impetigo or eczema) should be rigidly isolated in single rooms whenever possible.

(To be concluded)

REFERENCES

1. Aldrich, C. A. War comes home to pediatrics. *Am J Dis Child* 71:5 1946
2. Gesell, A., et al. *The First Five Years of Life: A guide to the study of the first school child from the Yale Clinic of Child Development*. 393 pp. New York: Harper & Bros., 1940
3. Gesell, A. L., and Ilg, F. L. *The Child from Five to Ten*. 475 pp. New York: Harper & Bros. 1946
4. The Academy Study of Child Health Services. academy study. *J Pediatr* 28:621 1946
5. Royal College of Physicians of London. Final Report of the Pediatric Committee, 1946. P. 2
6. Swenson, O., and Ladd, W. E. Surgical emergencies of alimentary tract of newborn. *Am Surg J Med* 233:660-665 1945
7. Gross, R. E. Surgical treatment for abnormalities of heart and great vessels. Beaumont lecture 1946 (in press)
8. Black, A., and Taussig, H. B. Surgical treatment of malformations of heart. *J A M A* 128:189-202, 1945
9. Diamond, L. K. Unpublished data.
10. Miller, H. C., Hurwitz, D., and Kuder, K. Fetal and neonatal mortality in pregnancies complicated by diabetes mellitus. *J A M A* 124:271-275 1944
11. Miller, H. C. Effect of prediabetic state on survival of fetus and birth weight of newborn infant. *Am Surg J Med* 233:376-378 1945
12. Miller, H. C. Effect of diabetic and prediabetic pregnancies on fetus and newborn infant. *J Pediatr* 29:455-461 1946
13. Bernstein, I., and Dolger, H. Fetal mortality in women during prediabetic period. *Am J Obst & Gynec* 51:420-422 1946
14. Warkany, J. Manifestations of prenatal nutritional deficiency. *Fetus and Horrors* 3:73-103 1945
15. Jackson, B., and Kintner, V. E. Relation between maternal vitamin A intake, blood level, and ocular abnormalities in offspring of rat. *Am J Ophthalmol* 29:1234-1242 1946
16. Butler, A. M., Ruffin, J. M., Sniffen, M. M., and Wickson, M. E. Nutritional status of civilians rescued from Japanese prison camps. *Am Surg J Med* 233:639-652, 1945
17. Smith, C. A. Unpublished data.
18. Coste, W. R., McCammon, C. S., and Christie, A. Congenital defects following maternal rubella. *Am J Dis Child* 70:301-306 1945
19. Prendergast, J. J. Congenital cataract and other anomalies following rubella in mother during pregnancy (California survey). *Arch Ophth* 53:39-41 1946
20. Goar, E. L., and Potts, C. R. Relationship of rubella in mother to congenital cataracts in child. *Am J Ophth* 29:566-569 1946
21. Cordes, F. C., and Barber, A. Changes in lens of embryo after rubella microscopic examination of eight-week-old embryo. *Arch Ophth* 36:135-140 1946
22. Fox, M. J., and Bortun, M. M. Rubella in pregnancy causing malformations in newborn. *J A M A* 130:568 1946
23. Arcock, W. L., and Ingalls, T. H. Maternal disease as principle in epidemiology of congenital anomalies with review of rubella. *Am J M Sc* 212:366-379 1946
24. Evans, M. W. Congenital dental defects in infants subsequent to maternal rubella during pregnancy. *M J Australia* 2:225-228 1944
25. Swan, C., and Tostevin, A. L. Congenital abnormalities following infectious diseases during pregnancy with special reference to rubella third series of cases. *M J Australia* 1:645-659 1946
26. Winterbotham, L. P. Congenital cardiac defects associated with maternal rubella. *M J Australia* 2:16-19 1946
27. Massachusetts Department of Public Health. Congenital defects due to rubella. *New Eng J Med* 235:53 1946
28. Wetzelhoft, C. Mumps its glandular and neurologic manifestations. In *Ferns and Rickettsial Diseases*. 507 pp. Cambridge: Harvard University Press 1940. Pp. 309-348
29. Lenne, M. I. Sponsored epidemic in private school. *Am J Pub Health* 34:1274-1276 1944
30. Edgar, G. E. Active immunization. *New Eng J Med* 235:256-265, 294-303 and 328-336 1946
31. Anderson, T., and McKenzie, P. Postvaccinal encephalitis. *Lancet* 2:667-669 1942
32. Anderson, J. F. Post vaccination tetanus studies on its relation to vaccine virus. *Pub Health Rep* 30:2111-2117 1945
33. Liebling, J., and Schmitz, H. E. Protection of infant against diphtheria during first year of life following active immunization of pregnant mother. *J Pediatr* 23:404-436 1945
34. Pratt, E. L. Clinical tetanus study of 56 cases with special reference to methods of prevention and plan for evaluating treatment. *J A M A* 129:1243-1247 1945
35. Jones, F. G., and Moss, J. M. Combined diphtheria and tetanus toxoid alum precipitated. *J Lab & Clin Med* 24:512-516 1939
36. Peshkin, M. M. Immunity to tetanus induced by third dose of toxoid two years after basic immunization based on study of thirty-one allergic children. *Am J Dis Child* 65:873-881 1943. Immunity to tetanus induced by third dose of toxoid three years after basic immunization based on study of thirty-eight allergic children. *Ibid* 67:22-29 1944. Immunity to tetanus induced by third dose of toxoid four years after basic immunization based on study of twenty-five allergic children. *Ibid* 69:83-88 1945
37. Felton, H. M., and Willard, C. Y. Current status of prophylaxis by hemophilus pertussis vaccine. *J A M A* 126:294-299 1944
38. Sauer, L. W. Age factor in active immunization against whooping cough. *Am J Pub Hlth* 17:719-723, 1941
39. Waddell, W. W., Jr., and Engle, C. S., Jr. Immune response to early administration of pertussis vaccine. *J Pediatr* 29:487-492, 1946
40. Sako, W. Studies in pertussis. *J Pediatr* 30:29-40 1947
41. Felton, H. M. Status of passive immunization and treatment in pertussis by use of human hyperimmune serum. *J A M A* 128:26-28 1945
42. Bradford, W. L., Scherph, H. W., and Brooks, A. M. Prophylactic value of refined antipertussis rabbit serum. *Proc Soc Exper Biol & Med* 49:157, 1942
43. Lapin, J. H. Serum in prophylaxis of contacts and treatment of whooping cough. *J Pediatr* 26:555-559 1945
44. McGuinness, A. C., Armstrong, J. G., and Felton, H. M. Hyperimmune whooping cough serum. *J Pediatr* 24:249-258 1944
45. Lapin, J. H. Mixed immunization in infancy and childhood. *J Pediatr* 22:439-451 1943
46. Miller, J. J., Jr., Humber, J. B., and Dourie, J. O. Immunization with combined diphtheria and tetanus toxoids (aluminum hydronate adsorbed) containing Hemophilus pertussis vaccine. *J Pediatr* 24:281-289 1944
47. Salk, J. E., Pearson, H. E., Brown, P. N., Smith, C. J., and Francis, T., Jr. Immunization against influenza with observations during epidemic of influenza A one year after vaccination. *Am J Hyg* 42:307-322 1943
48. Francis, T., Jr., Salk, J. E., and Brace, W. M. Protective effect of vaccination against epidemic influenza B. *J A M A* 131:275-278, 1946
49. Veldee, M. V., Pede, E. C., Franklin, J. P., and DuPuy, H. R. Dick reaction and scarlet fever morbidity following injections of purified and tannic acid precipitated erythrogenic toxin. *Pub Health Rep* 56:957-974 1941
50. Gordon, J. E. Personal communication.
51. Janeway, C. A. Clinical use of products of human plasma fractionation: albumin in shock and hypoproteinemia, gamma globulin in measles. *J A M A* 126:674-680 1944
52. Coburn, A. F., and Paul, R. H. Studies on immune response of rheumatic subject and its relationship to activity of rheumatic process: observations on reactions of rheumatic group to epidemic infection with hemolytic streptococcus of single type. *J Exper Med* 62:159-178 1935
53. Hansen, A. Rheumatic recrudescences: diagnosis and prevention. *J Pediatr* 28:296-303 1946
54. Watson, R. F., Rothbard, S., and Swift, H. F. Use of penicillin in rheumatic fever. *J A M A* 126:274-280 1944
55. Warren, H. A. Treatment of acute rheumatic fever with penicillin. *J A M A* 126:231, 1944
56. Favour, C. B., Janeway, C. A., Gibson, J. G. H., and Levine, S. A. Progress in treatment of subacute bacterial endocarditis. *New Eng J Med* 234:71-77 1946
57. Tortone, J., Chaitas, A., Myers, J. A., Stewart, C. A., and Strenkens, T. Tuberculosis in children less than six years of age. *Am J Dis Child* 58:92-101 1939
58. Bratley, M. E. Prognosis in white and colored tuberculous children according to initial chest x-ray findings. *Am. J Pub Health* 33:343-352 1943
59. Smith, C. A., and deLacey, W. Prognosis of infantile tuberculosis. *New Eng J Med* 222:215-217, 1940
60. Wallgren, A. Pulmonary tuberculosis: relation of childhood infection to disease in adults. *Lancet* 1:417-420 1938
61. Smith, C. A., Faulkner, W. H., and Cordi, J. M. Tuberculin tests in children: interpretation of series of varying intradermal test doses and of comparable series of patch tests. *New Eng J Med* 225:100-1013 1941
62. Hollander, A. Ultra-violet irradiation as means of disinfection of air. *Am J Pub Health* 33:980-984 1943
63. Hamburger, M., Robertson, O. H., and Pack, T. T. Present status of glycol vapors in air sterilization. *Am J M Sc* 209:162-166 1945
64. Loois, C. G., and Robertson, O. H. Recent studies on control of dust borne bacteria by treatment of floors and bedclothes with oil. *Am J M Sc* 209:166-172 1945

months of age. So far as plague and typhus are concerned, however, it is equally essential for the mother to know the endemic status of the disease in her area and to make sure that nursemaids, cooks and so forth are not carriers of the insect vectors involved. In general, the vaccines against typhoid fever, plague, cholera and typhus may be given to children by the same schedule as that for adults, half the adult dosage being used for children under five years of age. It should be remembered that

TABLE 1 *Mortality among Patients Contracting Tuberculosis in Childhood*

AUTHOR	TYPE OF INSTITUTION	AGE AT DISCOVERY OF TUBERCULOSIS	SUBSEQUENT MORTALITY FROM TUBERCULOSIS
		yr	%
Tortone ⁴⁷	Preventorium and case finding	1	10
		1-2	4
		3	3
Brasley ⁴⁸	Hospital and out-patient department	3	14
Smith ⁴⁹	Infants' hospital	2	34

stimulating doses must be given every six months for typhus and every four months for cholera and plague, and that immunization should be completed two weeks before the subject enters an endemic area.⁵⁰ The chance of exposure of infants to yellow fever is slight in urban areas, but immunization should probably be given when it is recommended by local health authorities, since lasting protection is thereby afforded.

The use of immune serum globulin in the prophylaxis of measles in exposed persons has become an established pediatric procedure. A dose of 0.1 cc per pound of body weight will prevent the disease in the great majority of cases, whereas 0.02 cc per pound of body weight will usually allow the patient to experience a modified attack. The globulin is given intramuscularly and should be administered in the first six days after exposure. The larger preventive dose should be used for children under three years of age or for sick, debilitated and tuberculous children, and modification should be attempted in all other healthy children who have been exposed to the disease. Modified measles, which is less severe and less apt to be followed by complications, probably gives relatively permanent immunity to most children.⁵¹

The prophylactic administration of chemotherapeutic drugs has a limited but definite place in preventive medicine. Certain groups of children — notably those who have had one or more attacks of rheumatic fever — run a serious risk of recurrence with an increase in cardiac damage if they contract an infection with Group A beta-hemolytic streptococci.⁵² Once they have recovered from their original attack of rheumatic fever, there are psychologic objections to removing these children from their normal environment. Since their homes or schools seldom experience a winter without the occurrence

of hemolytic streptococcus infection in some member of the group, there is a special risk for these children at home and at school. The use of prophylactic sulfadiazine — in doses of 0.25 gm twice a day to young children and of 0.5 gm twice a day to older children and adolescents — throughout the danger season (from October to June) has seemed to be helpful in diminishing the incidence of rheumatic recurrence.⁵³ The children should be carefully observed for rash or granulocytopenia particularly during the first six to eight weeks, when most of these reactions occur. If sulfadiazine-resistant organisms become more prevalent, this chemoprophylaxis will obviously be less effective, and studies with the use of oral penicillin will be necessary. At the moment its routine use for this purpose cannot be recommended and would be financially burdensome. Unfortunately, the penicillin treatment of established streptococcal infections has not seemed to prevent rheumatic fever or its recurrences or to affect the course of the disease once it has developed.^{54, 55}

Children with rheumatic heart disease or with congenital heart lesions, particularly patent ductus arteriosus or patent interventricular septum, should be given penicillin treatment whenever dental extractions or tonsillectomies are performed, in the hope that the development of subacute bacterial endocarditis will be prevented.⁵⁶ Ideally, treatment with full doses should be begun forty-eight hours before operation and continued for five days afterward. The responsibility of keeping the teeth of these patients in good condition is particularly great for the same reason.

The family physician is the person who can do most to control tuberculosis in childhood. The serious prognosis of primary tuberculosis in infancy is indicated in Table 1. The suspicion of tuberculosis in any adult in a home with children should immediately be followed up with x-ray examination. Now that milk is no longer a serious source of infection, tuberculosis in infants and children is almost invariably the result of household contact with an adult who is spreading tubercle bacilli.⁶⁰ The only way to prevent tuberculosis is to find all persons with positive sputums and remove them from contact with children. With the Vollmer patch test,⁶¹ tuberculin testing can be carried out routinely in children at intervals of a year, starting at six months of age. The emphasis, however, should be on the discovery of the adult who is the source of the infection, *before* the children become infected rather than afterward.

No discussion of the prevention of infectious disease in children would be complete without mention of the fact that hospitals remain discouragingly dangerous places for infants and children. Transmission of virulent bacteria from one child to another and from attendants takes place all too frequently. Epidemic diarrhea has proved to be even more readily communicable than the ordinary

and the QRS complex in Lead 3 was W-shaped. The T waves were upright in Leads 1 and 3 and slightly low in Lead 2, the ST segment in Lead CF₁ was slightly sagging, and the T wave was diphasic.

Three months before entry there was a marked increase in the substernal discomfort. Attacks of steady, crushing substernal pain radiating down both arms into the back and up the neck to the jaw were brought on by slight exertion, occurring about once a day and lasting about fifteen minutes at a time. A month later the patient developed a cough that was productive of white mucoid sputum and was particularly severe at night. A month before entry he was forced to stop working. The attacks had begun to occur even while he was resting, and he sometimes awoke with the sensation in the morning. The pain was so severe that he always had to stop whatever he was doing until it had subsided. At the time of entry he was having as many as four attacks a day and was practically bedridden. Mannoitol hexamitrate was of no avail. Nitroglycerin gave some relief but was followed in several hours by nausea and vomiting.

Physical examination disclosed an anxious patient who was repeatedly belching small quantities of air. The left fundus showed an occlusion of the superior temporal artery just off the disk, as evidenced by parallel ensheathing of the arterial walls for a distance of 1 or 2 disk diameters. Otherwise the vascular changes appeared if anything less severe than those on the first examination. The left border of the heart was in the anterior axillary line in the fifth and sixth interspaces. The aortic second sound was much louder than the pulmonic second. There was a questionable apical gallop. The lungs and abdomen were clear.

Examination of the blood showed a red-cell count of 5,310,000, with 15.0 gm of hemoglobin, and a white-cell count of 9200, with 80 per cent neutrophils. The urine had a specific gravity of 1.020 and gave a ++ test for albumin.

An electrocardiogram showed a sinus rhythm at a rate of 90 per minute. The S waves were sagging in Leads 1 and 2, and the T waves were sagging, low and diphasic in Leads 1 and 2, upright in Lead 3 and inverted in Lead CF₁, the ST segment was sagging in Lead CF₁.

On the second hospital day, during a bed bath, the patient suddenly complained of dizziness and lapsed into unconsciousness. When a physician arrived two minutes later the heart had ceased beating, and the patient was somewhat cyanotic. He emitted several gasps during the following three minutes. Despite the intracardiac administration of coramine the heart action could not be re-established.

DIFFERENTIAL DIAGNOSIS

Dr. EDWARD F. BLAND. This is in some respects a discouraging case but an important one. The pa-

tient died at twenty-seven years of age. At the age of twenty-three he had, by most criteria, malignant hypertension—at least, it was acute and severe, and there was beginning retinitis and choking of the optic disks. Renal function was somewhat impaired, although the concentrating power of the kidneys was good. If a patient with this situation appeared again tomorrow, we should consider him a candidate for an almost emergency sympathectomy. There may be some dissenting voices, however, on that score.

In looking back over the record, we are most interested in the evidence whether or not sympathectomy had any effect on this patient's subsequent course. The chief complaint on the first admission was headache, he was largely relieved of this symptom. It has been noted in many cases after sympathectomy, even though the high blood pressure in some cases has been only slightly or moderately ameliorated, that the relief of troublesome headaches has been striking. Furthermore, it is of special interest that four years later the renal function actually seemed a trifle better and the eye grounds were no worse, some observers even thought that they were better. In other words, it seems as though the sympathectomy, without influencing significantly the level of the blood pressure, had in some fashion protected both the eyes and the kidneys. A final point—if we can consider this clinically malignant hypertension, without necrotizing renal arteriolitis by biopsy—is that a twenty-three-year-old patient would have been expected to succumb in a few years in uremia. He died four years later, but not in uremia.

Is there anything that we need say about the differential diagnosis? In any person of this age with hypertension one should consider coarctation of the aorta, but presumably he did not have that. Nothing is said about the arterial pulsations in the legs or notching of the ribs on x-ray study, but almost certainly if abnormal these would have been mentioned. A condition that might be considered in passing is a paraganglioma. The hypertension was not paroxysmal, but we know that perhaps 10 per cent of patients who have hypertension secondary to paraganglioma have sustained hypertension. If such a lesion had been present it would probably have been discovered at operation, since it is routine to search carefully for these tumors, they are not always found in the immediate vicinity of the kidney, however. We are not told the reaction of his blood pressure to change in posture. Dr. Smithwick* has recently pointed out that if the hypertension is due to a tumor of this type the blood pressure falls in a striking fashion when the patient shifts from a recumbent to a standing position. He has studied only a few cases, but that seems to be the pattern. In the case under discussion we have no reason to think that the hypertension was secondary to tumor.

*Smithwick R. H. Unpublished data.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 33231

PRESENTATION OF CASE

First admission A twenty-three-year-old machinist entered the hospital two months after he had been rejected by his Selective Service board because of hypertension.

The patient had been in perfect health until a year before entry, when he began to have a "tired feeling" and discomfort in the low back, which he attributed to overwork and long hours of standing, it occurred about once in three or four weeks and was relieved by rest. At the same time frontal headaches also developed, occurring about once a week and lasting four or five hours. Six months before entry he first noticed easy fatigability.

The patient was in good physical condition but appeared apprehensive. The fundi showed borderline blurring of the disks and diffuse narrowing of all the retinal arteries, there was little arteriovenous nicking. The diastolic blood pressure in the retinal arteries was 65. There was a loud, snapping aortic second sound, and a blowing apical systolic murmur, which was not transmitted. The pulse was bounding. Examination of the lungs and abdomen was negative.

The temperature, pulse and respirations were normal. The blood pressure was 245 systolic, 160 diastolic.

Examination of the blood showed a hemoglobin of 87 per cent and a white-cell count of 11,250. The nonprotein nitrogen was 38 mg., and the cholesterol 170 mg. per 100 cc. A blood Hinton test was negative. The urine gave a ++ test for albumin, but the sediment did not contain cells or casts. A phenolsulfonephthalein test showed 51 per cent excretion of the dye in 2 hours. The maximum specific gravity in the urinary concentration test was 1.018.

X-ray films of the chest showed a cardiothoracic ratio of 12.5:28.5. The left ventricular area was somewhat blunted, and the aortic knob slightly more prominent than normal. An intravenous pyelogram showed little dye excretion on the right, this was repeated and confirmed. The left kidney appeared normal. There were some calcified pelvic arteries. A retrograde pyelogram was normal.

An electrocardiogram showed a normal rhythm, a rate of 85 per minute and a PR interval of 0.16 second. The T waves were inverted in Lead 3, low and notched in Lead 4 and low in Lead 1. A sedation test reduced the blood pressure to 150 systolic, 110 diastolic.

A left lumbar sympathectomy was performed with removal of the sympathetic trunks from the fifth dorsal to the second lumbar segment inclusive. Following the operation the patient developed a serosanguineous effusion in the left side of the chest but recovered satisfactorily and was discharged on the forty-first hospital day.

Second admission (three weeks later) The patient was readmitted for a right lumbar sympathectomy.

At operation the right kidney was found to be grossly normal, but a biopsy was reported as showing nephrosclerosis, Grade III. At discharge the blood pressure while the patient was standing was 165 systolic, 110 diastolic.

Final admission (four years later) The patient was followed in the Out Patient Department. Six months after discharge the blood pressure had returned to 230 systolic, 140 diastolic. He felt well, however, and the headaches had almost disappeared. Eight months after discharge he returned to work. Two years before entry the main complaints were lack of libido and insomnia. He worked eight hours a day and experienced fatigue only after particularly great effort. The blood pressure when the patient was lying down was 240 systolic, 135 diastolic. The insomnia was finally controlled with phenobarbital. Potassium thiocyanate was used to treat the hypertension but was discontinued by the patient because of postprandial pains across the chest and down the left arm to the elbow. A year and a half before entry he began to have episodes of precordial "squeezing" sensations, occasionally radiating down both arms and occurring several times a month when he was walking or climbing stairs or after eating. After a few minutes of rest the feeling disappeared. The blood pressure at that time was 270 systolic, 170 diastolic, and he was occasionally found to have a gallop rhythm. His working time had been reduced to six hours. Five months before entry a chest film showed a cardiothoracic ratio of 14:29, as well as some prominence in the region of the left ventricle.

The lung fields were clear except for some blunting of the right costophrenic angle. An intravenous pyelogram showed prompt excretion of dye on both sides. A phenolsulfonephthalein test showed 63 per cent excretion of the dye in 2 hours. The urine had a specific gravity of 1.020 and was free of albumin. The nonprotein nitrogen was normal. An electrocardiogram showed a sinus rhythm and a rate of 90. The PR interval was 0.17 second, and the QRS complex 0.08. The axis and voltage were normal. There was prominence of the ST segment in Lead 2,

thectomy might be given credit for having exerted a protective action on the kidneys, because the patient did not develop progressive renal failure. It is true that death in uremia with the post-mortem finding of necrotizing renal arteriolitis is the expected end-result in patients who conform to Fahr's original criteria for the diagnosis of malignant hypertension, but this unfortunate term has been redefined in so many different ways during the past twenty years that there are now no generally accepted minimum criteria for a clinical diagnosis of malignant hypertension. In this case, the diagnosis seems to have been based mainly on the patient's age and the finding of "questionable blurring of the optic disks." Even if the diagnosis of malignant hypertension is accepted, however, it does not seem justifiable to assume that the untreated course would inevitably have led to progressive renal failure, and therefore to suggest that sympathectomy exerted a protective action on the kidneys because renal failure did not occur. On the contrary, it seems to me that there is nothing in the history of this case that is incompatible with the assumption that the operation had no significant beneficial effect on the progress of the disease, which ran a fairly rapid course from accidental discovery to death in a period of four years.

In conclusion, I should like to make it clear that my remarks are not intended to convey the impression that sympathectomy should not have been performed on this patient, or that it should not be given a trial in other cases of a similar nature. On the contrary, the shortcomings of other methods of treatment are so obvious that it seems perfectly reasonable to proceed with the operation, merely because one can offer little else that may be expected to exert a beneficial effect on the course of the disease. I believe, however, that we can hope to arrive at an accurate evaluation of the real therapeutic effectiveness of sympathectomy in the treatment of hypertension only if we analyze the results in each case with the maximum degree of objectivity.

CLINICAL DIAGNOSES

Malignant essential hypertension
Hypertensive heart disease
Cardiac arrest

DR. BLAND'S DIAGNOSES

Essential hypertension, severe
Hypertensive and coronary heart disease
Angina pectoris decubitus
Lumbodorsal sympathectomy

ANATOMICAL DIAGNOSES

Arteriosclerosis, coronary, severe, with extreme narrowing
Cardiac hypertrophy and dilatation, slight
Myocardial infarcts, focal, old and recent

Arteriolar nephrosclerosis, severe right, minimal left
Arterial and arteriolar sclerosis, generalized, moderate

Operations: bilateral lumbodorsal sympathectomy, old

PATHOLOGICAL DISCUSSION

DR. MALLORY: Interest naturally centers on the histologic findings in the kidneys. At the time of the sympathectomy, biopsies were done on both kidneys. It will be recalled that the right kidney had shown possible evidence of impaired function, if the intravenous pyelogram is to be credited. Later, however, the dye excretion improved on that side. The biopsy of the right kidney showed quite marked arteriolar changes, which we classified as Grade III, whereas the biopsy from the left kidney showed only Grade I changes. At autopsy the same degree of difference was apparent on the two sides, although there was progression of both. Even the more severely involved kidney showed no necrotizing arteriolitis.

The other findings were approximately as expected. The heart showed moderate hypertrophy, weighing 430 gm. The major coronary arteries were severely sclerotic, and the lumens reduced to pin points—in some places there was no lumen. There was no major infarction of the heart, but the myocardium presented evidence of some focal old scarring and also evidence of numerous small spots of fresh necrosis of cardiac muscle that had the appearance of being two to four days old. This fresh necrosis coincided with the period of terminal entry to the hospital. The lungs showed chronic passive congestion.

CASE 33232

PRESENTATION OF CASE

A forty-nine-year-old man entered the hospital because of retrosternal and epigastric pain.

Three and a half hours before admission, during a heated argument, the patient was suddenly seized by a pain in the neck, at about the level of the thyroid cartilage. He was forced to sit down and was unable to talk or breathe properly for about fifteen minutes. During that time the pain gradually traveled downward anteriorly in the midline to the upper abdomen and finally settled in the left upper quadrant, radiating through the body to the angle of the left scapula. It remained constant in the retrosternal and abdominal location, until the time of admission. No nausea, vomiting, hemoptysis or other symptoms accompanied this attack. Three days prior to admission the patient had slipped and fallen on a curbstone, with considerable resulting pain and ecchymoses and swelling of the left leg. In addition, for ten days he had had a slight cough productive of whitish sputum in which there were occasional small amounts of blood.

The final condition that we might consider is primary renal disease on the basis of pyelonephritis in the past, with renal injury. We have no real evidence to suggest this. The retrograde pyelograms showed no irregularity in contour of the ureters, pelves and calyces, and there was no indication of chronic renal infection. Therefore, we must dismiss these other possibilities and say that this was a case of essential hypertension occurring acutely and severely in a relatively young person. He ultimately died of severe angina pectoris on the basis of coronary disease. At the final admission he did not live long enough to have special studies or therapy instituted. I suspect that those in charge were at somewhat of a loss regarding just what therapy to institute. In addition to nitrates and oxygen, he was probably given digitalis, because of the cardiac enlargement and weakness (gallop rhythm). If he had survived long enough it might have been helpful to have him on a rice diet or at least on a low-sodium regime. If he had improved a little on that and yet continued to have intractable angina pectoris, one might have seriously considered a thoracic sympathectomy for relief of pain.

The cause of this patient's sudden exitus was almost certainly cardiac and not cerebral. It was too abrupt for a cerebral accident. The heart was not beating when the physician, who presumably was nearby at the time, arrived a moment later. Perhaps acute coronary insufficiency is as good an explanation clinically as anything else. For a final diagnosis I believe that he had severe essential hypertension, hypertensive and coronary heart disease and angina pectoris decubitus. He ran a progressively downhill course, so far as the hypertension and coronary disease are concerned, and yet I am forced to think that he received some benefit from the sympathectomy regarding protection of the kidneys and eyes and certainly relief from headaches. Whether or not it was worth while in this case is debatable, but I should strongly recommend the same procedure if faced with a similar situation.

DR ROBERT S PALMER Dr Bland has summarized this case extremely well. In young patients like this, with a high diastolic pressure and early papilledema, we have seen the best results from sympathectomy, provided that cardiac and renal functions are seriously impaired. There have been 3 such patients, three to five years after operation, with normal or nearly normal blood pressures. Two other similar patients, who were considered to have malignant hypertension when operated on three and five years ago, are alive and working, although again hypertensive. One is working in a grocery handling heavy goods. Unfortunately, persistent high diastolic pressures are often associated with diffuse arteriolar disease. There was some evidence of this in the case under discussion. I think that this patient was probably relieved, that his

life was prolonged and that the renal function may have been spared. Dr Bland mentioned emergency sympathectomy. Delay may be costly, since renal damage may advance rapidly, seemingly in a matter of days. I think that I have seen the entire course of malignant hypertension from symptomatic onset to death in five or six weeks. Rarely, there may be such a thing as emergency sympathectomy to spare kidney damage.

DR BENJAMIN CASTLEMAN How often have you seen the onset of angina following sympathectomy in patients who have never had it before?

DR PALMER I do not know. This is certainly an outstanding example. I have had the impression that some people with dorsolumbar sympathectomy and resulting postural hypotension have been relieved of angina even when high dorsal sympathectomy was not done, but I cannot speak definitely on this point.

DR WALTER BAUER What right have you to say that sympathectomy will prevent irreversible uremia? There are many other reasons to prevent irreversible kidney lesions.

DR PALMER If I said what Dr Bauer says I did it was a rash statement, and I am glad to be corrected. If the patient is operated on, the operation should be done before serious impairment of renal function sets in. It seems that some of our patients closely similar to this, have continued a long time without progressive kidney change, whereas patients with malignant hypertension who have not had sympathectomy, as Dr Bland has pointed out often have progressive changes in the kidneys and die in uremia. I should point out that it is remarkable for a person with this type of hypertension to have gone so long without more kidney damage. I am not sure, from the qualitative tests of renal function, that positive improvement in renal function was demonstrated.

DR TRACY B MALLORY Dr Evelyn, will you express your views on the subject?

DR KENNETH A EVELYN In this case, as in many similar cases that have been reported in the literature, I find it difficult to accept the evidence brought forward in support of the claim that sympathectomy has a specific ability to relieve headache even in patients in whom the operation fails to produce a significant lowering of the blood pressure. It is well known that relief of symptoms in hypertensive patients may occur after a variety of nonspecific therapeutic measures, including venesection and psychotherapy, but when there has been no reduction of blood pressure it does not seem justifiable to ascribe any specific virtue to sympathectomy in this regard. In any event, in this particular patient, headache was a relatively minor complaint even before the operation.

My second comment concerns the diagnosis of malignant hypertension in this patient and the validity of Dr Bland's suggestion that the sympha-

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DIFFERENTIAL DIAGNOSIS

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FIGURE 3

some disease of the leg veins. Prolonged, severe and widespread pain of this type, however, is not characteristic of that condition, and the absence of tachycardia and dyspnea essentially excludes such a diagnosis. In this patient pain was the cardinal symptom, with embolism to the lung, on the other hand, shortness of breath is usually predominant, and there may be no pain at all. Furthermore, definite evidences of a peripheral phlebitis are lacking, and there were no x-ray signs of pulmonary infarction.

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Several diagnoses that come to mind should be mentioned for the sake of completeness but appear unlikely. The sudden onset of severe chest pain suggests a spontaneous pneumothorax, but the physical and x-ray findings allow us to rule out such a possibility. Mediastinal emphysema may also be eliminated on the same grounds. Pulmonary embolism is suggested by the history of trauma to one leg, by the sudden onset and by the evidence of

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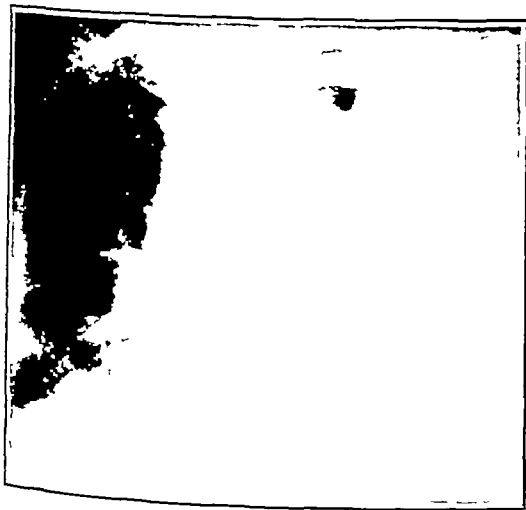


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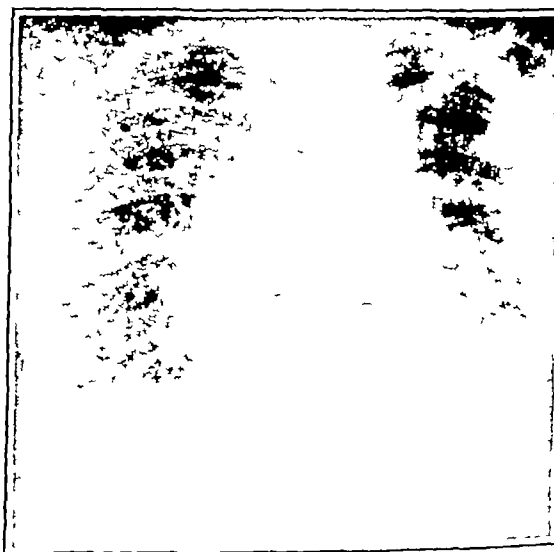


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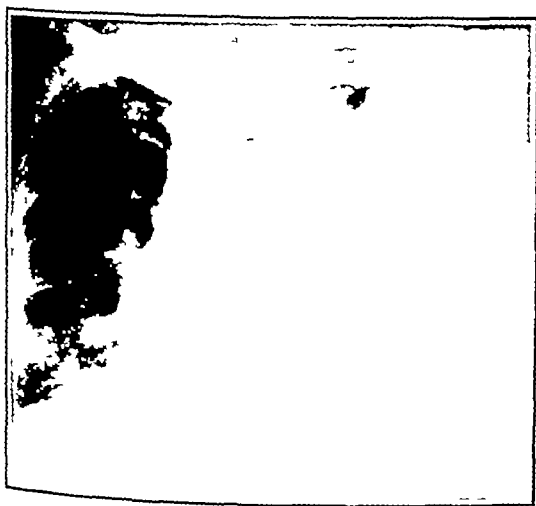


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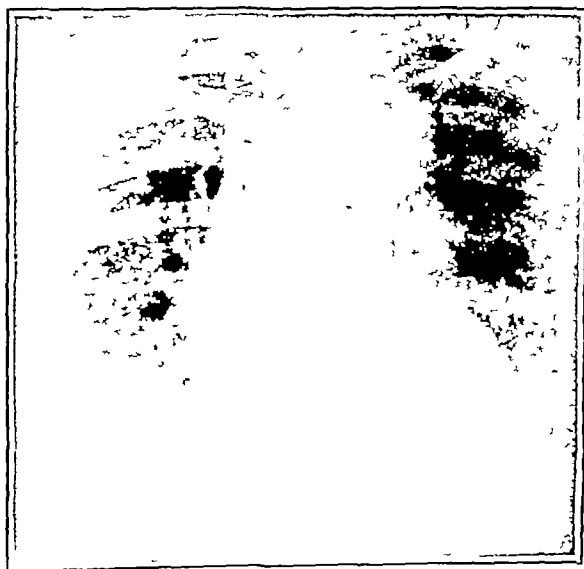


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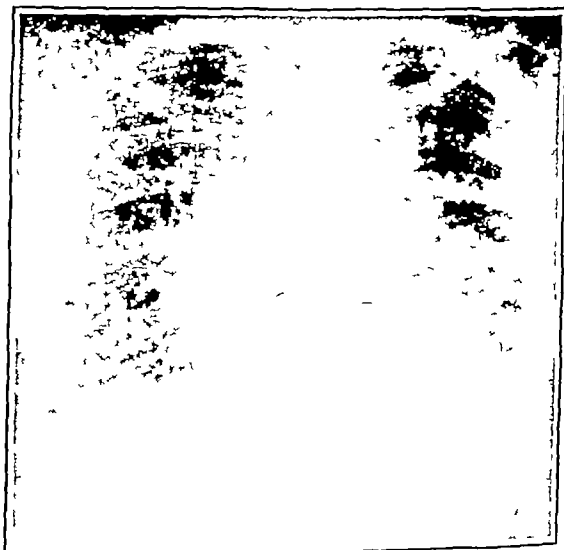


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The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

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Material should be received not later than noon on Thursday three weeks before date of publication.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

ONE HUNDRED AND SIXTY-SIXTH ANNIVERSARY

THE one hundred and sixty-sixth anniversary of the Massachusetts Medical Society, held at the Hotel Statler, Boston, on May 20, 21 and 22 was a highly successful affair. The total registration—1521—although not so large as that of last year, was impressive, and all who were present, including fellows, speakers, and exhibitors, seemed to be more than satisfied.

The annual meeting of the Council was held on the evening of May 19. Practically all committee reports, together with their recommendations, were routinely accepted on the basis of approval by the Executive Committee. Two matters are of general interest. Dr. Humphrey L. McCarthy, chairman

of the Committee to Meet with General Hawley, reported that the scheme whereby medical care to veterans was to have been covered by a contract between the Blue Shield and the Veterans Administration had been blocked. He suggested that the Society deal directly with the Veterans Administration under a gentleman's agreement, similar to the so-called 'Kansas Plan,' and the motions necessary to reopen the matter were passed by the Council. Under "new business," Dr. Merrill C. Sosman presented resolutions adopted jointly by several groups of radiologists, anesthesiologists and pathologists relative to the all-inclusive coverage of hospital services by the new contracts of the Blue Cross, which became effective on June 1. These organizations oppose any arrangement by a hospital with Massachusetts Hospital Service that permits the latter to guide or determine professional services, oppose the principle of comprehensive coverage on a per-diem basis of compensation because it fails to distinguish between hospital and professional services and recommend that charges for all professional services should be specifically excluded from all hospital-service plans. After the Council had voted to suspend its rules for procedure, approval of these resolutions was voted. The officers elected for the current year are as follows: president, Edward P. Bagg, president-elect, Daniel B. Rear-don, vice-president, Charles J. Kichham, secretary, Joseph Garland, treasurer, Eliot Hubbard, Jr., assistant treasurer, Norman A. Welch, ^{orator} Allen S. Johnson ^{going for all reserve Board and}

At the annual meeting, ^{there} ^{unanimously agreed} spreading the debt widely, Dr. Dwight O'Hara after ^{plans and more by individuals} inspiring talk covering "The Plan, which is currently being read the names of eleven ^{man or woman, the business} and automatic saving heretofore the Society in 1897 ^{and employees on payroll savings} ^{this plan} commercial banks will invite their depos- ^{on a card provided by the bank, to direct the bank to} ^{ke a monthly deduction equivalent to the purchase price} as a Series E, F or G Savings Bond. The bank makes the de- ^{duction} charges the account for the purchase price and, ^{during the month} mails the bond to the customer. The de- ^{ductions may be discontinued at any time by authorization} ^{The plan combines a way to invest regularly in the best} ^{possible security and at the same time to help in the wise debt} ^{management so essential to the national welfare.} ^{The Bond-a-Month Plan deserves serious consideration} ^{Further details may be obtained at one's bank.}

ORVILLE S. POLA, D
State Director

U. S. Savings Bonds Division
Treasury Department
79 Milk Street
Boston 9

I should interpret the terminal episode as one of rupture of the column of blood through the adventitia of the aorta into the left pleural cavity, producing a slow steady leak. The chest x-ray findings might best be explained on that basis. Whether or not the aorta also ruptured into the pericardium I do not know. There is actually no necessity for assuming that it did. The presence of good pulsations in the dorsalis pedis artery bilaterally indicates that the dissection probably did not extend down to the common iliac arteries. I am unable to correlate such a diagnosis with the possibility of rheumatic heart disease and with the history of hemoptysis. The patient could have had mitral stenosis, if so, it must have been incidental and not a factor in the final illness.

I shall, therefore, make a diagnosis of a dissecting aneurysm secondary to a cystic necrosis of the media of the aorta.

DR MILFORD D SCHULZ The films of the chest made on entry show a tortuous and somewhat widened aorta, which can still be traced fairly well to the diaphragm. Twenty-four hours later the mid-portion of the descending aorta has become irregular in outline and is lost in an ill defined shadow that extends to each side of the mediastinum. A film made four days later shows fluid in the left pleural sinus, the mediastinum seems to be slightly wide and irregular, and the descending aorta is completely lost. The widening of the mediastinum, the irregularity of the aortic shadow and the loss of its contour can certainly be explained by hemorrhage into the mediastinum or into the wall of the aorta, which subsequently escaped into the left chest.

CLINICAL DIAGNOSIS

Dissecting aneurysm of aorta

DR PAUL'S DIAGNOSIS

Dissecting aneurysm of aorta, with rupture into left pleural cavity

ANATOMICAL DIAGNOSES

Dissecting aneurysm of aorta, with rupture into left pleural cavity
Cardiac hypertrophy, hypertensive type

PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN This man had a aortic dissection. The intimal tear occurred in the arch close to the origin of the left subclavian artery and the dissection had progressed from this point distally down to but not involving the iliac arteries. There was some dissection up the left common carotid and subclavian arteries but no involvement of the renal or mesenteric vessels. The exact point of external rupture could not be determined, but it was obvious as soon as the chest was opened that the rupture had occurred into the left pleural cavity because the latter was filled with both clotted and unclotted blood. From the history we know that the external tear had begun six hours before death and was therefore not a large one. There was enough time for some of the blood to extend extrapleurally into the retroperitoneal tissues around the upper abdominal aorta — even to surround the left adrenal cortex on its upper and posterior surfaces.

As usually observed, there was slight arteriosclerosis of the aortic intima, the cause of the dissection being medial necrosis cystica. The heart was hypertrophied, weighing 630 gm.

It is interesting to note that this man's symptoms correlate strikingly with the anatomic findings. The initial tear was in the left arch, with dissection up the left great vessels, and the initial symptom was pain in the neck. The dissection went down the descending aorta, thus accounting for the abdominal symptoms. There was practically no chest pain, which corresponds with the absence of dissection in the ascending aorta, unlike the great majority of cases of aortic dissection, in which the ascending portion is involved.

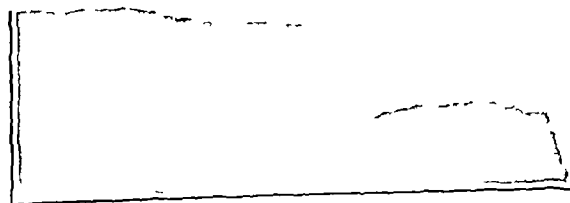


FIGURE 1

admission and another five days later showed changes consistent with left-axis deviation, no indication of infarction was observed in either film. Shortly after admission the serum amylase level was 20 units, and the nonprotein nitrogen 23 mg per 100 cc.

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His widow, a son, two daughters, two sisters, a brother and a grandson survive.

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CORRESPONDENCE

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To the Editor—The Massachusetts Department of Labor and Industries has recently passed rules and regulations designed to prevent anthrax in industries where animal products are handled. This step was taken after a survey of these plants by the supervising industrial inspector of the Division of Industrial Safety and the physician of the Division of Occupational Hygiene. The survey followed what might be called an "epidemic" of anthrax among the workers in four relatively small concerns handling hair and wool. Within the year there were seven cases with four deaths.

Study of collected data shows that in Massachusetts between 1933 and 1940, there were 34 cases of anthrax with 4 deaths, a mortality of 12 per cent, while from 1940 to 1945, there were 21 cases with 7 deaths, a mortality of 33 per cent. The increase of the disease on the part of physicians outside the State serving in the tanneries of Massachusetts appeared to be the greatest factor in this high mortality rate. Lack of knowledge of the worker and his employer regarding the malignant character of anthrax was also a serious factor. Finally, it seems quite naturally see little of this disease and, in experience, have been unaware of the heroic measures necessary for its successful treatment. Penicillin fortunately appears to be specific therapy if given early and in large doses.

The following table analyzing the work of the anthrax virus is of importance in bringing out these facts:

TYPE OF WORK	NO OF CASES	NO OF DEATHS	MORTALITY %
Tannery	5	1	3
Hair and bristle	7	5	71
Wool	7	3	43
Transportation	4	2	50
Agriculture	2	0	0
	55	11	

Section 9 of the rules and regulations requires the employer to engage a competent physician aware of the anthrax hazard and further to arrange that a worker "with any sore, boil or pimple" on the exposed parts of his body be immediately seen by the designated physician. The remainder of the rules implement this regulation and outline required washing facilities.

Unfortunately, there is no known practical method of destroying anthrax spores in animal products for industrial use without interfering with the commercial value of the material. Animal products imported into this country from the Orient, South America and Europe, notably central European countries, are potential sources of anthrax. Furthermore, recent information from the Veterinary Section of the United States Public Health Service states that anthrax spores occur in the soil and hence on the animals of all but five states in this country, with the heaviest contamination in Texas, Louisiana, South Dakota and California.

There are no interstate quarantine laws for regulating the distribution of anthrax infected animal products. Federal inspection of imported animal material, formerly carried out by the Bureau of Animal Industry, has been discontinued, since animal anthrax in this country is controlled by anthrax vaccine. Unfortunately, the anthrax vaccine does not rid the animal's hide and hair of anthrax spores, nor is there an anthrax vaccine available for human use.

An understanding of the problem by employer, worker and physician should eliminate fatalities in industries where anthrax is a hazard.

A copy of these rules and regulations may be obtained by writing or phoning the Massachusetts Division of Occupational Hygiene, 286 Congress Street, Boston 10 (phone, LIBerty 0183).

HARRIET L. HARDY, M.D.

Physician, Division of Occupational Hygiene

286 Congress Street
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BOND-A-MONTH PLAN

To the Editor—The national debt amounts to \$1840 for each man, woman and child in America. The management of this debt will affect prices, employment, wages, how much people can buy and what their savings will be worth. It will affect everyone in his work and at his dinner table.

Wise management of the debt will help level off the economic peaks and valleys that make rough going for all. The Treasury Department, the Federal Reserve Board and the American Bankers Association are unanimously agreed that wise management includes spreading the debt widely, that is, fewer bonds held by banks and more by individuals.

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State Director

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College of Medicine, and director of the Medical Service, College Division, King's County Hospital, Brooklyn, New York. This paper, entitled "Clinical Significance of Circulatory Peculiarities of Some of the Vital Organs," was published in the May 22 issue of the *Journal*.

The annual dinner was attended by 418 fellows and guests. The principal speaker was Dr. Shoulders, who spoke on the topic, "The Responsibilities of the Medical Profession."

The scientific sessions were well attended, as were the section meetings and the exhibits. The paucity of scientific exhibits was unfortunate but necessitated by a cutting down of the space permitted. It is to be hoped that in the future some arrangement can be made whereby a larger number of such exhibits can be accommodated.

Dr. Sidney C. Wiggin, the other members of the Committee on Arrangements and Mr. Robert St. B. Boyd, executive secretary of the Society, deserve great praise for making possible a meeting that was so successful.

ANTHRAX

ALTHOUGH relatively few physicians have ever seen a case of anthrax in their practices, the disease does occur with enough frequency to constitute a true occupational hazard, particularly in a state like Massachusetts in which the handling of hides, wool

Dissection of animal products is widespread in industry. Left pleural elsewhere in this issue of the to the fact that from 1940 cases of anthrax, with 7 per cent. Furthermore, it these fatalities could

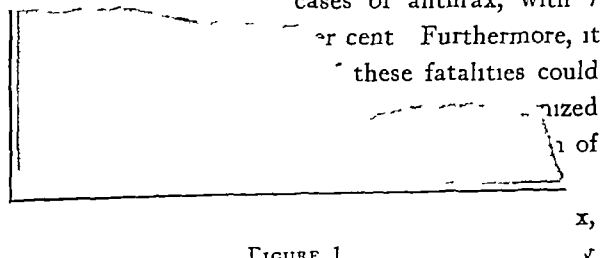


FIGURE 1

admission and another five days later showed changes consistent with left-axis deviation, no indication of infarction was observed in either film. Shortly after admission the serum amylase level was 20 units, and the nonprotein nitrogen 23 mg per 100 cc.

tion of animal products, such as hides, skins, wool hair, bones, bristles and so forth. These rules and regulations chiefly concern measures to prevent anthrax, such as dust control, the maintenance of clean and sanitary conditions in the plant, and washing facilities, adequate protective covering and individual clothes lockers for employees, as well as a drying room for work clothes. In addition, a responsible plant official is required to arrange for immediate medical attention in all suspected cases, each employee must report any "sore, boil or pimple" and all suspicious lesions must be seen by a designated physician who has "a thorough knowledge of the problems of anthrax." Failure to conform to the statute is punishable by fine.

Undoubtedly most of these requirements have been met for many years by large industrial firms, such as tanneries, in which the employers, employees and company physicians are fully aware of the anthrax hazard. But in small concerns and in those in which the disease occurs infrequently proper precautions have not been taken, and when anthrax has appeared, it has not been diagnosed early enough in the majority of cases for treatment to be as effective as it should be. These new rules and regulations, if properly enforced, should go far in lowering the morbidity and mortality of the disease.

REFERENCES

1. Murphy, F. D., Boccetta, A. C., and Lockwood, J. S. Treatment of human anthrax with penicillin: report of three cases. *J. A. M. A.* 126: 948-950, 1944.
2. Lucchesi, P. F., and Gildersleeve, N. Treatment of anthrax. *J. A. M. A.* 116: 1506-1508, 1941.

MASSACHUSETTS MEDICAL SOCIETY

BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups, such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of dates can be avoided.

DEATHS

DAY — Hilbert F. Day, M.D., of Cambridge, died May 16. He was in his sixty-ninth year. Dr. Day received his degree from Harvard Medical School in 1905. For thirty years he was surgeon-in-chief of the Boston Dispensary. He was a member of the board and a former president of the Washingtonian Hospital and honorary

President of the Cambridge Tuberculosis and Health Association. For twenty years he taught at Harvard Medical School, and since 1934 he had been clinical professor of surgery at Tufts College Medical School. Dr Day was a member of the New England Obstetrical and Gynecological Society and the New England Pediatric Society and a fellow of the American College of Surgeons and the American Medical Association.

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Agriculture	4	0	0
	55	11	

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Study of collected data shows that in Massachusetts between 1935 and 1940, there were 34 cases of anthrax with 4 deaths, a mortality of 12 per cent, while from 1940 to 1945, there were 21 cases with 7 deaths, a mortality of 33 per cent. Ignorance of the disease on the part of physicians outside those serving in the tanneries of Massachusetts appeared to be the greatest factor in this high mortality rate. Lack of knowledge of the worker and his employer regarding the malignant character of anthrax was also a serious factor. Finally, physicians quite naturally see little of this disease and, in our experience, have been unaware of the heroic measures necessary for its successful treatment. Penicillin fortunately appears to be specific therapy if given early and in large doses for a long period.

The following table analyzing the work of the anthrax victims is of importance in bringing out these facts:

RESTORATION OF LICENSES

To the Editor At a meeting of the Board of Registration in Medicine held May 16, it was voted to restore the registration to practice medicine to Dr Julius Shubert, 26 Esmond Street, Dorchester, whose registration was revoked June 6, 1945

H QUIMBY GALLUPE, M D, *Secretary*

State House
Boston

To the Editor At a meeting of the Board of Registration in Medicine held May 16, it was voted to restore the registration to practice medicine to Dr Aaron O Bernstein, formerly of 98 Main Street, Gardner, whose registration was revoked June 7, 1945

H QUIMBY GALLUPE, M D, *Secretary*

State House
Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Obstetrical Practice By Alfred C Beck, M D, professor of obstetrics and gynecology, Long Island College of Medicine and obstetrician and gynecologist-in-chief, Long Island College Hospital. Fourth edition. 4°, cloth, 966 pp., with 1068 illustrations. Baltimore: Williams and Wilkins Company, 1947. \$7.00

This standard textbook by an outstanding authority in his field first published in 1935 and translated into Portuguese in 1940, has been revised to bring the text up to date. The sections on implantation and placentation have been rewritten and simplified. The use of penicillin in the prevention of congenital syphilis is discussed in the sections on syphilis and pregnancy and puerperal infection. A new chapter on analgesia, amnesia and anesthesia has been added. The picture of Dr Oliver Wendell Holmes shows him as an old man. One taken about 1843 would have been more suitable. A list of selected references is appended to each chapter. The text is printed with a good type, and the illustrations are adequate. The price is surprisingly low for the size of the volume. The book is recommended for all medical libraries.

Essentials of Endocrinology By Arthur Grollman, Ph D, M D, professor of medicine and chairman, Department of Experimental Medicine, Southwestern Medical College, and attending physician and consultant in endocrinology, Parkland Hospital, Dallas, Texas. Second edition, revised and enlarged. 8°, cloth, 644 pp., with 132 illustrations. Philadelphia: J B Lippincott Company, 1947. \$10.00

This standard work, first published in 1941, has been revised to include new material published during the past six years. Emphasis has been placed on the clinical aspects of endocrinologic disorders in which most of the recent advances have been made.

The material is well organized, and each chapter is documented with a select list of references to the recent literature, analyzed in the text. The book is well published. The type is especially good, and the illustrations are excellent. The volume is heavy for its size, owing to the use of coated paper, and special tables of endocrinologic products are printed on the inside linings of the front and back covers—an unfor-

tunate practice for valuable material. The volume should be in all medical libraries for reference purposes and should prove useful to physicians interested in the subject.

Synopsis of Operative Surgery By H E Mobley, M D, chief in surgery, St Anthony's Hospital, Merrilton, Arkansas. Second edition. 8°, cloth, 416 pp., with 383 illustrations, including 37 in color. St. Louis: C V Mosby Company, 1947. \$6.00

This manual for students of surgery, first published in 1940, has been revised and brought up to date. The beginning chapters are devoted to anesthesia, postoperative care and surgical technic, and the others to major operations. The drawings are clear and well executed. The material is well arranged and well printed, although the type is small. The manual should prove useful as a reference book for students and surgeons. The price seems excessive for the size of the volume.

The Head, Neck, and Trunk Muscles and motor points By Daniel P Quiring, Ph D, head of Anatomy Division, Cleveland Clinic Foundation, and associate professor of biology, Western Reserve University. 8°, cloth, 115 pp., with 101 illustrations. Philadelphia: Lea and Febiger, 1947. \$2.75

This small book is designed as a companion volume to the author's *The Extremities*, previously noted in the *Journal*. The individual muscles of the head, neck and trunk are portrayed, together with their chief arterial and nerve supply. The diagrams are excellent and based on original dissections and on references to standard anatomies. The volume should be useful to students and physical therapists, and to surgeons for reference purposes.

Ulcer of the Stomach, Duodenum, and Jejunum By Ralph C Brown, M D, Professor of Medicine, University of Illinois College of Medicine, and attending physician, Presbyterian Hospital, Chicago. 8°, cloth, 172 pp. with 40 illustrations. New York: Oxford University Press, 1946. \$2.25 (Reprinted from *Oxford Loose-Leaf Medicine*).

The author in this small book discusses the pathology, symptoms, diagnosis and treatment of peptic ulcer in the light of the latest knowledge of the subject. Special emphasis is placed on differential diagnosis and treatment. The book should prove useful to physicians in general practice.

Diseases of the Nose and Throat By Charles J Imperator, M D, consulting laryngologist, Harlem Hospital and Nyack General Hospital, and consulting bronchoscopist, Manhattan Eye, Ear and Throat Hospital, Flower and Fifth Avenue Hospitals, and Riker's Island Hospital, and Herman J Burman, M D, director, Department of Otolaryngology, Harlem Hospital, instructor in otolaryngology, Columbia University College of Physicians and Surgeons, and assistant visiting otolaryngologist, Presbyterian Hospital and Vanderbilt Clinic. Third edition. 8°, cloth, 576 pp., with 480 illustrations. Philadelphia: J B Lippincott Company, 1947. \$12.00

This standard textbook, first published in 1935 and translated into Spanish in 1942, has been revised to incorporate the advances in the subject since the publication of the second edition in 1939. A new section on the vitamins has been added, and the use of penicillin and the sulfonamides has been discussed especially in relation to intracranial complication. The chapter on radiation therapy has been completely revised and brought up to date. The material is well organized. A two-column format is used to save paper, but the type and printing are good and the volume is well published. The book is recommended to medical libraries as a reference source.

(Notices on page xviii)

The New England Journal of Medicine

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Volume 236

JUNE 12, 1947

Number 24

THE SURGERY OF CANCER*

CHARLES HUGGINS, M D †

CHICAGO

LET us stand back for a moment and inspect the edifice of knowledge already erected on the surgery of cancer. This paper considers the history of the basic concepts involved in the modern surgery of tumors and attempts to demonstrate the inter-relation in the growth of these ideas, this perspective will permit a prognosis to be uttered for the surgical discipline in cancer. Obviously all three efforts must be brief and sketchy, a list of all the contributors to cancer surgery would read like the catalogue of the ships in the second book of the Bible or the begat series in Genesis.

I suppose that a defense of the historical approach is never necessary. Although its methods are occasionally tiresome to nonprofessional historians, history is often of interest, and it becomes important if one can see in past performance a clue for future advance.

It might well be asked why the surgery of cancer should be discussed at a celebration of the introduction of anesthesia. There are several reasons — the development of the modern concepts of neoplastic disease was coeval with and largely consequent on the development of modern surgery. Clearly, before pain had been controlled and the relaxation of muscles had been secured, surgical operations on internal organs were possible to such a limited extent as to be practically negligible. Certainly, the surgery of tumors of the viscera comprises a large percentage of the surgical task and the opening of this field awaited anesthesia for its development. Also, the famous operation that introduced the use of ether in surgery was performed by Dr. Warren on a vascular tumor of the neck.

A century ago cancer was emerging from a period of empiricism and superstition in which the disease had been completely shrouded in mystery. Some attempts at description of tumors had been made, but medicine was in the Paleozoic age, innocent of laboratories and nearly devoid of the correlation of

the clinical state with dead-house findings, despite Morgagni's *De Sedibus*.¹ Before 1846 few studies of cells or tissues had been made, and cellular pathology was unknown. At that time, in his second published paper entitled "Weisses Blut," Virchow had just attributed correctly the pale character of the blood in leukemia to an excess of white corpuscles.

As representative of early American surgical thought about neoplasms I cite the experience of Warren,² who in 1839 described the status of cancer surgery at the Massachusetts General Hospital just before the discovery of anesthesia. He stated that an "exact discrimination between different kinds of tumors is very important to the practitioner of surgery." He added "The opinion he may offer in such cases will soon be put to a severe and public test, for the course of these diseases lies open to the view of the patient and his friends and the result must be known to them." At that time, however, so little was known about disease that diagnosis was often impossible. The differentiation, for example, between granulomas and neoplasm was difficult, although scrofulous lesions were well recognized. Cancer, according to Warren, was not regarded as a specific disease. "It has a variety of forms, of causes and of habitudes of action. There is nothing specific in it unless you call its incurable disposition specific." A constitutional predisposition to cancer was recognized, and the disease was thought to occur frequently after violence. Tobacco was recognized as a factor in lesions of the mouth and lower lip.

Two species of cancer were regarded as separate entities easily distinguishable from each other — namely, carcinoma and fungoides. Carcinoma, or scirrhus, was characterized by its hardness and its tendency to ulceration. The term "fungoides" (sarcoma) was used for tumors that were soft and had a tendency to bleed easily.

In cancer of the breast Dr. Warren recognized that "enlargement of the glands in the axilla commonly took place from the extensions of the diseased action along the absorbent vessels," and that

*Presented at the Ether Day Centenary of the Massachusetts General Hospital, Boston, October 14, 1946.
†From the Department of Surgery, School of Medicine, University of Chicago.

†Professor of surgery (urology) School of Medicine, University of Chicago.

when the lymph nodes were enlarged the disease was usually incurable. Thyroid tumors were believed to be a disease of inland countries and of territories situated on the banks of rivers, and the recommended treatment was the internal use of burnt sponge and of iodine. Tumors were frequently of tremendous size before operation was undertaken, often weighing ten to twenty pounds.

The surgical treatment, which was largely superficial, was confined to tumors of the head, except for the cranial contents, and the neck, breast, extremities and skin. Strong men had important roles in the operation as technical assistants. Extensive operations on the jaws were often undertaken. The surgical procedures were threefold, consisting of excision, mass ligation with stout cords transfixing the tumors at right angles by the aid of needles either straight or crooked or the actual cautery. In procedures of excision skin flaps were raised when possible and resutured loosely at the end of the operation. Bleeding and air embolism often provided a serious difficulty.

The modern reader is impressed by three characteristics of preanesthetic surgery: the deficiency of pathological knowledge at that time, the often reckless celerity of the surgical procedure and its attendant agonies. The surgeons of a hundred years ago were men of intelligence whose mental powers we can, with charity, rate equal to our own. Was everything that they did inferior to the practices of today? Obviously not, one gains the opinion that in anatomic knowledge, at least, the surgeon was rather better informed than the average surgeon today, since anatomic dissection was nearly the only investigative outlet for diligent and thoughtful surgeons.

The necessity for rapid operations required that the procedure be well thought out. The following advice of Warren is still apposite to surgical practice:

An operator should not be satisfied with tracing a plan in his mind only. It should be fairly written out, and he should imagine all possible difficulties and embarrassments and put them in writing.

The evolution of the surgery of cancer from this elementary position was biphasic and rested on the development of some working concepts of the disease, as well as on the establishment of better surgical ideas. Both aspects had to be developed simultaneously, since both required much the same methods—the methods of science. Progress in medicine has always been dependent on the advances of pure science to a peculiar extent. A secondary or reading knowledge of science has usually provided an insufficient stimulus for the discovery or application of scientific knowledge to the clinical problems. Working with phenomena gives a vastly more intimate familiarity with the effects of nature than books do, and for this reason the greatest advances in medicine have been made

by active participants in research. Also, the scientific indoctrination of close observation and precise thought has provided a fresher attitude to the puzzles of medicine than was possible with bedside study alone. These are concepts of primary importance because they provide historical justification for the necessity of surgical laboratories and research workers in the clinical departments.

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The concept of organization of the body in cellular units depended on the development of the achromatic microscope by Silligues, of Paris, in 1824. Müller³ himself soon undertook the microscopic study of cancer cells (his findings were published in 1838), but the morphologic studies of that time were at a primitive level. In 1852 one of his students, Adolf Hannover,⁴ of Copenhagen, set cancer of the skin apart from other cancers because of its low rate of growth and coined the name "epithelioma" for this group of neoplasms, which he regarded as more benign than the tumors of the viscera. Another of the contributions of Hannover was the advocacy of biopsy of superficial lesions to establish a pathological diagnosis. Rudolf Virchow,⁵ who graduated from the University of Berlin in 1843, was another of Müller's pupils who exerted a great influence on pathology—indeed, he was one of the fathers of this discipline. Virchow's great contribution was the recognition of the importance of the cell in pathological processes. Before Virchow the cellular structure of cancerous tissue had been recognized, but the cell had been thought to be subsidiary to an underlying humoral "blastema," which was regarded as a sort of primary fluid from which all structures arose. Haagensen⁷ estimates Virchow's discovery as follows: "With his dictum 'Omnis cellula e cellula' Virchow swept away this erroneous conception and firmly established the cell as the fundamental unit in which disease processes operate." This law, which states that all living cells represented an uninterrupted continuum, has had functional value in the elucidation of disease. No one has been able to disprove it, and it has been largely unquestioned recently, although it is probably wrong. Perhaps, in some of the back waters and bayous of the world molecular conjunctions are occurring to effect reproducibility or life.

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Advances in the general field of surgery made possible the surgical treatment of external cancers, but the development of surgical technics for the treatment of internal cancer required the discovery and application of the principles of surgery. The formulation of the principles of surgery made tremendous strides in the last century and is still going on. These principles are probably not yet definitive or insusceptible of clarification, and consequently they cannot be regarded as a finished product incapable of improvement.

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when the lymph nodes were enlarged the disease was usually incurable. Thyroid tumors were believed to be a disease of inland countries and of territories situated on the banks of rivers, and the recommended treatment was the internal use of burnt sponge and of iodine. Tumors were frequently of tremendous size before operation was undertaken, often weighing ten to twenty pounds.

The surgical treatment, which was largely superficial, was confined to tumors of the head, except for the cranial contents, and the neck, breast, extremities and skin. Strong men had important roles in the operation as technical assistants. Extensive operations on the jaws were often undertaken. The surgical procedures were threefold, consisting of excision, mass ligation with stout cords transfixing the tumors at right angles by the aid of needles either straight or crooked or the actual cautery. In procedures of excision skin flaps were raised when possible and resutured loosely at the end of the operation. Bleeding and air embolism often provided a serious difficulty.

The modern reader is impressed by three characteristics of preanesthetic surgery: the deficiency of pathological knowledge at that time, the often reckless celerity of the surgical procedure and its attendant agonies. The surgeons of a hundred years ago were men of intelligence whose mental powers we can, with charity, rate equal to our own. Was everything that they did inferior to the practices of today? Obviously not, one gains the opinion that in anatomic knowledge, at least, the surgeon was rather better informed than the average surgeon today, since anatomic dissection was nearly the only investigative outlet for diligent and thoughtful surgeons.

The necessity for rapid operations required that the procedure be well thought out. The following advice of Warren is still apposite to surgical practice:

An operator should not be satisfied with tracing a plan in his mind only. It should be fairly written out, and he should imagine all possible difficulties and embarrassments and put them in writing.

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protoplasm and that the chemical reactions and functions of this jelly of the cells are of considerable significance to him

Of particular importance in cancer surgery is the recognition of a neoplasm through accurate diagnosis and in an early stage of the life of the tumor. Clearly, the surgery of advanced tumors is a pessimistic performance. The diagnosis awaited physical and chemical means for its development. The physical instruments of greatest value were the electric lamp of Edison and the x-rays of Roentgen¹⁷ (1895). The application of tiny electric lamps to the cystoscope by Nitze¹⁸ in 1887 made endoscopic cystoscopy possible and led to the development of urology as a specialty. The discovery influenced medicine considerably, and Nitze acknowledged in his first paper that the diagnosis of bladder tumors was the great triumph of his method. Menlo Park also made possible direct examination of the rectum, sigmoid, stomach, esophagus, bronchi and other previously inaccessible regions. The impact of Roentgen's discovery on diagnosis was so large as to be incalculable and its use revolutionized the detection of disease in every field of medicine.

Chemistry has also contributed to the diagnosis of surgical disease, especially in cancer. Indirect methods concern concentration of radio-opaque dyes in the gall bladder and urinary tract as introduced by Graham and Cole¹⁹ (1924) and Binz²⁰ (1930) respectively. Direct methods of chemical diagnosis of cancer are concerned with the urinary excretion of proteins derived from cancer cells, such as the albumose of Bence-Jones²¹ (1848) in multiple myeloma, of melanin in melanosarcoma and of chorionic gonadotropin in testicular tumor as discovered by Zondek²² in 1930. In prostatic cancer tumor products are also detectable in the blood in the form of certain enzymes, as demonstrated by Gutman and Gutman²³ in 1938. Since the aim of diagnosis is to recognize disease without seeing the patient, it is clear that the laboratory must assume large importance as the science develops.

The surgical problems of cancer were largely brought into focus and the principles of surgical treatment developed in the evolution of the handling of patients with cancer of the female breast. This was natural for several reasons, especially because mammary cancer is frequent. Contributory also were the facts that the primary lesion and the lymph nodes draining the breast were superficial and easy to examine and that the surgical treatment did not involve violation of a body cavity. In 1867 Moore,²⁴ of London, was one of the first surgeons to appreciate that the recurrence of a breast cancer was due to incomplete removal of the tumor, it had previously been thought that these lesions represented an entirely new neoplasm developing on an organic or constitutional basis. Moore proposed that when the adjoining skin or axillary lymph nodes are involved by cancer they should be removed in one

mass, since it is desirable to avoid cutting into the tumor or even exposing it at operation.

The value of this concept of block dissection was confirmed and the technic widened by Volkman who discovered that cancer cells frequently infiltrated the fascia covering the pectoralis major muscle so that this fascia was routinely removed by him. Halsted¹⁴ (1890) showed that technically the best way to do this was to remove the pectoral muscles, and he also advocated the removal of large amounts of skin surrounding the tumor. Each technic resulted in a larger percentage of cures than previously, and axillary dissection became a routine whether or not the lymph nodes were suspected of being grossly involved by the tumor.

The surgery of visceral cancer was developed in a definite time sequence — namely, abdominal and genitourinary tracts, central nervous system and lastly the chest.

Visceral surgery could not be developed before anesthesia or antiseptics, but with these aids the essential methods were rapidly introduced. The principal methodology of abdominal surgery was devised largely in the Billroth school in Vienna. Theodor Billroth was a magnetic leader and a tireless and intelligent worker as well as a *bon vivant*. His school worked out many of the technics of stomach and bowel resection on animals in the surgical laboratory, and this approach in itself was a contribution to surgical investigation of first-class importance. In 1881 Billroth²⁵ made the first resection of the pylorus for gastric cancer and performed many intestinal resections between 1878 and 1883. A Billroth pupil, Anton Wölfler,²⁶ devised the technic of gastroenterostomy in 1881, and another student, Mikulicz²⁷ (1903) introduced obstructive resection with exteriorization of the large bowel for carcinoma, both procedures advanced cancer surgery. Surgeons throughout the world soon added many technical refinements to abdominal surgical technic.

Tumors of the urinary tract were seldom treated before the advent of precise diagnostic methods. The first tumor of the bladder to be removed by *sectio alta* was operated on by Billroth²⁸ in 1872, the diagnosis having been made by urethrotomy with digital palpation of the neoplasm in the vesical cavity. Cystoscopy, ureteral catheterization and pyelography converted a *terra incognita* into a field characterized by diagnostic precision. Although the electrically lighted cystoscope of Nitze had made possible the diagnosis of bladder tumors, Nitze had unsuccessfully tried to catheterize the ureters, since he had no way of manipulating the tip of the catheter. A remarkably interesting Cuban, Joaquin Albarran,²⁹ professor of urology in Paris, solved this problem by devising a cystoscope with a movable arm to provide leverage and thus to guide the catheter into the ureteral ostium. Ureteral catheterization and the subsequent introduction of contra-

radiography by Voelcker and von Lichtenberg³⁰ (1903) were real steps forward in the diagnosis of renal neoplasms. The perineal approach to the prostate and total prostatectomy introduced by Young³¹ (1906) made possible the excision of early cancer of the prostate gland. The introduction of high-frequency currents and their application to cystoscopic fulguration by Beer³² have added much to the treatment of vesical neoplasms.

The surgery of tumors of the nervous system was developed chiefly because of the efforts of the Queen Square group in London and of Cushing³³ and Dandy^{34, 35} in the United States. In 1885 Bennett and Godlee³⁶ first localized and removed a brain tumor, although unfortunately the wound in this case became infected and the patient died a month later of meningitis. Gowers and Horsley³⁷ in 1888, first localized and extirpated a tumor of the spinal cord, the patient making a complete recovery.³⁸ The contributions of Cushing³³ in the field of tumors of the nervous system were manifold, perhaps his most significant contributions were the development of a refined deliberate surgical technic, new approaches for the cerebellar tumors and a classification of neoplasms of the brain. The Cushing methods transformed what was previously a highly dangerous operative attack into a comparatively safe one. The fertile mind of another Hopkins product, Walter Dandy,^{34, 35} contributed the diagnostic tools of encephalography and ventriculography and devised many clever procedures — for example, a new surgical approach for the treatment of tumors of the acoustic nerve.

The development of the surgery of intrathoracic neoplasms was delayed until methods were found to prevent pulmonary collapse. The solutions offered for the problem became progressively simpler. In the research laboratory of an industrial concern today there is a sign that reads as follows: "When the solution of your problem is known, it will be found to be simple." Methods of preventing collapse of the lung, such as the differential pressure cabinets of Sauerbruch,³⁹ were cumbersome and difficult to use and were soon replaced by intratracheal intubation, the present methods of dispensing anesthetic gases from tanks under pressure allow the lung to be kept at any required degree of expansion or collapse by the use of a simple facial mask.

Partial pneumonectomy for tumors of the lung was accomplished by Sauerbruch³⁹ in 1926 and by Churchill⁴⁰ in 1933 with good results, and the entire lung was first removed for cancer by Graham and Sager⁴¹ in 1933. In the early cases fear of the huge empty pleural cavity was present, and the space was obliterated by thoracoplasty, this was a groundless fear, however, and Rienhoff⁴² (1933) showed that the cavity became obliterated by compensatory pulmonary expansion, so that plastic operations on the chest wall were dispensable.

The surgical treatment of tumors of the thoracic esophagus was late in development. In 1913 the first successful esophagectomy was carried out in New York by Torek,⁴³ who resected the esophagus, bringing the proximal portion externally through a cervical incision and feeding the patient by gastrostomy. This technical procedure was superseded by the work of the Japanese surgeon Ohsawa,⁴⁴ who in 1934 performed successful transthoracic resection of the neoplasms of the esophagus and of the cardia of the stomach with esophagojejunostomy. This procedure has been refined and made less dangerous by the work of many thoracic surgeons, especially in America.

In orthopedic surgery the development of basic principles has influenced the surgery of bone sarcoma. Codman recognized the fact that giant-cell tumors of bone were benign lesions that did not require amputation of the limb. In 1938 Phemister⁴⁵ discovered that malignant bone sarcomas could often be cured by local resection of the involved part with preservation of the extremity through bone grafting. This is in accord with the ideas of modern cancer surgery — that is, there is no need to cut off the head to cure a brain tumor.

In the nineteenth century surgeons were concerned with descriptive pathology, with concepts of the grosser aspects of cancer and with the evolution of some of the simpler principles of surgery. With the close of this period the gross description of tumors had been rather well made, and the era of laboratory experimentation was fairly begun. Until disease can be reproduced in the laboratory, advances other than the descriptive ones — and description is necessarily limited in scope — must be uncertain and irregular. In the present century the chief achievements have been in the experimental production of tumors, in their treatment with radiant energy and in the beginning of chemotherapy. Owing to refinements in technic, tumors of nearly all the viscera have become surgically accessible. Evidently, most of the major technical obstacles of the anatomy and physiology involved in the approach to cancer in whatever locus have been solved.

In the research laboratories remarkable strides have been made since 1900. Transplantable tumors have become available since the work of Jensen⁴⁶ in 1903, and a wide variety of tumors of chickens, rabbits, rodents and frogs have been discovered. The viruses have been seriously implicated in certain neoplasms, as first shown by Rous⁴⁷ in 1911. The production of cancer in the laboratory with pure chemicals has been achieved.⁴⁸ The endocrine basis and methods for the experimental production of breast cancer have been discovered.

The diagnosis of tumors by chemical means was mentioned above. This is the newest and a promising field in cancer research, and it is striving to fill a grave hiatus. The importance of chemical investigation of the activity of tumors is that they

provide a measure. The greatest handicap to research on cancer is the lack of a yardstick—something that can be measured at daily intervals. This can be done only for tumors of the blood-forming organs, for osteogenic sarcoma and for cancer of the prostate.

Another of the recent developments in cancer is the chemical treatment of neoplasms of epithelial and hemopoietic tissues. Some progress has been made in the chemotherapy of prostatic and breast cancer, in which improvement has been profound and prolonged in many cases. Remissions of advanced neoplasms are being produced by chemotherapy. Although the treatment of carcinoma by medicines has been exceedingly limited, enough progress has been made so that it may be predicted with confidence that the medical therapy of cancer will increase in the future.

Therefore, I can now approach the somewhat delicate question of the prognosis of the surgery of cancer, realizing that prognosis and prophecy bear a close relation. The technical accomplishments of the surgeons have been brilliant and splendid but only when the lesion is essentially localized. The inherent defect in the surgical method is the impossibility of removal of widespread neoplasms, and the prognosis for treatment by classic surgery in metastatic cancer is poor. Nothing, however, stands in the way of surgical research on neoplasia, and much information may be expected from the surgical laboratories.

The constantly expanding significance, for the advance of medicine, of the research laboratory conducted in connection with a surgical clinic has been repeatedly emphasized. Since the surgical departments at present have greatest access to and often the greatest interest in the clinical course of patients with cancer, it is essential that the surgical laboratory take the lead in converting the surgery of cancer into medical treatment—this self-effacement being in keeping with the great tradition of surgery.

Fortunately, the avenues of research provide unlimited scope for constructive thought, and the technics of surgery applied to research problems in cancer may be developed to a high state of intellectual polish. At the risk of sounding hortatory, I wish to say that it devolves on the surgeons to make more investigation of tumors in their broader aspects. The researches are not without interest, and the opportunity to contribute to medicine through participation in investigations on cancer is large, hence, the prognosis for the broad surgical discipline in cancer is excellent.

REFERENCES

- Morgagni G B. *De sedibus et causis morborum per anatomen indagatis libri quinque*. 2 vol. Venice Remondiniana 1761.
- Warren J C. *Surgical Observations on Tumors with Cases and Operations*. 607 pp. Boston: Crocker and Brewster, 1837.
- Müller, J. *Über den feinem Bau und die Formen der krankhaften Geschwülste*. 60 pp. Berlin: G. Reimer, 1838.
- Hannover A. *Das Epithelioma, eine eigenthümliche Geschwulst die man im Allgemeinen bisher als Krebs angesehen hat*. 149 pp. Leipzig: L. Voss, 1852.
- Virchow R. *Weisses Blut. Neue Notizen aus dem Gebiete der Natur und Heilkunde*. 36, 151, 1845.
- Idem. *Die Cellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelehre*. 440 pp. Berlin: A. Hirschwald, 1858.
- Haagenensen C D. Exhibit of important books, papers, and memorabilia illustrating evolution of knowledge of cancer. *Am J Cancer* 18:42, 126, 1933.
- Thiersch, C. *Der Epithelsarkom, namentlich der Haut. Eine anatomisch klinische Untersuchung*. 310 pp. Leipzig: W. Engelmann, 1865.
- Waldeyer W. Die Entwicklung der Carcinome. *Firchow's Arch f path Anat* 55:67, 159, 1872.
- Lister, J. On new method of treating compound fracture, abscess etc. with observations on conditions of suppuration. *Lancet* 1:326-329, 357-359, 387, 389 and 507, 509, 1867.
- Idem. On new method of treating compound fracture abscess etc. preliminary notice on abscess. *Lancet* 2:95, 1867.
- von Bergmann E. Zur Sublimatfrage. *Therap Monatsschr* 14:44, 1887.
- Domagk G. Ein Beitrag zur Chemotherapie der bakteriellen Infektionen. *Deutsche med Wchnschr* 61:250, 253, 1935.
- Halsted, W S. Treatment of wounds with special reference to value of blood clot in management of dead spaces. *Johns Hopkins Hosp Rep* 2:255, 303, 1890.
- Landsteiner K. Über Agglutinationserscheinungen normalen menschlichen Blutes. *Wiener klin Wchnschr* 14:1132, 1134, 1901.
- Cannon, P R, Wissler R W, Woolridge R L, and Benditt E P. Relationship of protein deficiency to surgical infection. *Ann Surg* 120:514-525, 1944.
- Roentgen W C. Über eine neue Art von Strahlen. *Sitzungs d phys-med Gesellsch z Würzburg* 132:141, 1895.
- Nitze M. Beiträge zur Endoscopie der männlichen Harnblase. *Arch f klin Chir* 36:661-732, 1887.
- Graham E A, and Cole W H. Roentgenologic examination of gallbladder: preliminary report of new method utilizing intra venous injection of tetrabromphenolphthalein. *J A M A* 82:613, 1924.
- Binz A, Rath, C, and von Lichtenberg, A. Die Wiedergabe von Nieren und Harnwegen im Röntgenbilde durch Jodpyridinderivate. *Ztschr f ang Chem* 43:452-455, 1930.
- Bence-Jones H. On new substance occurring in urine of patient with mollities ossium. *Phil Tr London* 1:55-62, 1848.
- Zondek B. Über die Hormone des Hypophysenvorderlappens: Follikelreifungshormon (Prolan A) und Tumoren. *Klin Wchnschr* 9:679-682, 1930.
- Gutman A B, and Gutman E B. "Acid" phosphatase occurring in serum of patients with metastasizing carcinoma of prostate gland. *J Clin Investigation* 17:473-478, 1938.
- Moore C H. On influence of inadequate operations on theory of cancer. *Med-Chir Tr* 50:245-280, 1867.
- Billroth T. Offenes Schreiben an Herrn Dr L. Wittelschofer. *Wchnschr* 31:161-163, 1881.
- Wölfler, A. Gastro-Enterostomie. *Centralbl f Chir* 8:705, 708, 1881.
- von Mikulicz-Adamski J. Chirurgische Erfahrungen über das Darmcarcinom. *Arch f klin Chir* 69:28-47, 1903.
- Billroth T. Cited by Gussenbauer, C. Excision eines Harnblasenmyoms nach vorausgehendem tiefen und hohen Blasenschnitt. *Heilung. Arch klin Chir* 18:411-423, 1875.
- Albarán, J. Un nouveau cystoscope urétral. Applications du cathétérisme des uréters. *Comptes-Rendus du XII Congrès International de Médecine, Moscou 1897*. 5:209, 216, 1899.
- Voelcker F and von Lichtenberg A. Die Gestalt der menschlichen Harnblase im Röntgenbilde. *München med Wchnschr* 52:1576-1578, 1905.
- Young H H. Early diagnosis and radical cure of carcinoma of prostate: being study of 40 cases and presentation of radical operation which was carried out in 4 cases and appendix compiled later, containing complete histories of 64 cases. *Johns Hopkins Hosp Rep* 14:485-628, 1906.
- Beer E. Removal of neoplasms of urinary bladder: new method employing high frequency (Oudin) currents through catheterizing cystoscope. *J A M A* 54:1768, 1910.
- Cushing H. *Intracranial Tumors. Notes upon a series of two thousand verified cases with surgical mortality percentages pertaining thereto*. 150 pp. Springfield: Charles C Thomas, 1932.
- Dandy W E. Ventriculography following injection of air into cerebral ventricles. *Ann Surg* 68:5, 11, 1918.
- Idem. Röntgenography of brain after injection of air into spinal column. *Ann Surg* 70:397-403, 1919.
- Bennett, A H and Godlee R J. Case of cerebral tumour. *Med-Chir Tr* 68:242, 275, 1885.
- Gowers W R and Horsley V. Case of tumour of spinal cord: removal: recovery. *Med-Chir Tr* 71:377-430, 1888.
- Horsley V. Remarks on ten consecutive cases of operations upon brain and cranial cavity to illustrate details and safety of method employed. *Brit M J* 1:863-865, 1887.
- Sauerbruch, F. Die operative Entfernung von Lungengeschwülsten. *Zentralbl f Chir* 53:852, 857, 1926.
- Churchill E D. Surgical treatment of carcinoma of lung. *J Thoracic Surg* 2:254-266, 1933.
- Graham, E A and Singer J J. Successful removal of entire lung for carcinoma of bronchus. *J A M A* 101:1371, 1374, 1933.

42. Rehfuss W. F., Jr. Pneumonec-tomy, preliminary report of operative technique in 2 successful cases. *Bull Johns Hopkins Hosp.* 53: 9-10, 1933.

43. Tork, F. First successful case of resection of thoracic portion of esophagus for carcinoma. *Surg. Gynec. & Obst.* 16: 614-617, 1913.

44. Olszewski, T. *The Surgery of the Esophagus*. 95 pp. Kyoto, Kyoto Imperial University, 1934.

45. Phemister D. B. Bone transplantation in treatment of tumors and dystrophies of bones. *Ser. 1^{er} et 2^{es} de chir.* XI Congrès 1: 357-70, 1908.

46. Jensen C. O. Experimentelle Untersuchungen über Krebs bei Mäusen. *Centralbl. f. Bakteriol.* 34: 28, 1905.

47. Rous P. Sarcoma of fowl transmissible by agent separable from tumor cells. *J. Exper. Med.* 13: 97-111, 1911.

48. Yamagawa K., and Ichikawa K. Über die künstliche Erzeugung von Karzinom. *Verhandl. d. japan. ges. Gerichtlich.* 6: 169-178, 1916.

OBSERVATIONS ON A FAMILY EPIDEMIC OF INFECTIOUS HEPATITIS*

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An epidemic of infectious hepatitis occurring in 9 of 10 children in a single family was followed for five months in New York City. Such a high incidence of the disease in a group is unique in itself; in addition, these cases offered special information on four separate aspects of the disease — namely, epidemiology, the comparative value of certain liver-function tests, the occurrence of spider angiomas in the acute stage of infectious hepatitis and the incidence of subicteric cases.

All members of the family were observed in the Outpatient Department of the Rockefeller Hospital where liver-function tests were performed at regular intervals; 3 were admitted to the hospital for special studies. Friends of the family who came in contact with the children were also observed; 2 of this group were hospitalized with infectious hepatitis. The chief source of information regarding the illness of the children was the mother of the family, a trained nurse familiar with liver disease.

Several descriptions of family epidemics of infectious hepatitis have appeared in the literature in recent years.¹⁻⁴ The mode of spread in these families was generally believed to be droplet infection. Recent work on human volunteers has shown that the disease can be transmitted experimentally to man by parenteral injection of small amounts of infective serum, by ingestion of infective serum or feces and by the spraying of infective feces into the nasopharyngeal passages.⁵⁻⁷

During an epidemic in a summer camp, Neefe and Stokes⁸ found the virus of infectious hepatitis in the drinking water. This work, together with that of others,^{9, 10} indicates that contaminated water may be the source of infection in certain epidemics. Milk and food have also been implicated in a few outbreaks.^{11, 12} A characteristic of epidemics begun by contaminated food or water is their explosive nature, although sporadic cases often followed. Most of the epidemics described in the literature, however, are characterized by the serial occurrence of cases over a period of several months with a history of contact between the majority of patients. Some-

times, the contact appeared to be slight, and this led to postulation of droplet and air-borne infection. In view of the recent comparatively easy transmission of the disease in human volunteers by infective fecal material, spread by contact now seems more probable. The family epidemic under consideration in this paper offers certain information on this subject.

Brief summaries of the case records are as follows:

CASE 1. On November 15, 1945, this 10-year-old girl developed nausea, vomiting, abdominal pain and fever. These symptoms persisted for 2 days and were followed by a period of anorexia that lasted for 1 week. Considerable fatigue was noted, and the patient was forced to stay out of school for 10 days. Recovery was rapid and except for a weight loss of 7 pounds the patient felt fine by November 20. No jaundice was noticed.

Physical examination on January 26 disclosed a definite spider angioma over the left shoulder that blanched well on pressure. The liver and spleen were not palpable or tender. Liver-function tests revealed no abnormalities. On March 26 there were no changes except that the spider angioma had decreased in size and no longer blanched on pressure. On August 8 the angioma had completely disappeared.

CASE 2. On November 19, 1945, this 8-year-old boy developed pain in the upper abdomen and a loss of appetite that persisted for 2 days. A definite tenderness in the upper right side of the abdomen was noted by his mother. He stayed out of school for 1 day. Several nosebleeds occurred at that time — these were the first that had ever been noted. Recovery was rapid, and there were no further complaints. No jaundice was noticed.

Liver-function tests on January 25 disclosed no abnormalities.

Physical examination on January 26 revealed that the liver and spleen were not palpable or tender. Two definite spider angiomas were visible, one on the neck and one on the left shoulder, one showed blanching on pressure. On March 25 no changes were noted, except that both spider angiomas were slightly less distinct, but they were still noticeable, neither showed blanching on pressure. Physical examination on August 8 showed two small red spots still visible at the site of the spider angiomas, they no longer had the shape of a spider and did not blanch on pressure.

CASE 3. On November 25, 1945, this 6-year-old boy developed a moderate diarrhea that was followed by considerable pain and tenderness in the right upper abdomen. Some nausea and anorexia were present but no vomiting. No jaundice was noticed. He recovered uneventfully except for slight pain over the liver area that persisted for several weeks. He stayed out of school for 5 days because of illness.

Physical examination on January 26, 1946, showed that the liver and spleen were not palpable or tender. Seven definite spider angiomas were found over the arms and shoulders, four of them blanched on pressure. Determinations of bromsulphalein retention and plasma bilirubin were normal. The thymol-turbidity values were as follows: on January 26,

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11 units, on February 20, 10 units, on March 25, 6 units, and on August 8, 4 units

On March 25 the liver and spleen were not palpable or tender. Five of the seven spider angiomas were still present, but they had faded considerably, only one blanched on pressure. On August 8 two small spider angiomas were still visible, one blanched on pressure. Red spots remained at the sites of two old spider angiomas.

CASE 4 On December 22, 1945, this 15-year-old boy developed nausea, anorexia and vomiting, which lasted for 2 days. He also complained of soreness over the abdomen and of nosebleeds. He continued to go to school, however. Recovery was uneventful except for persistent soreness over the abdomen that caused him to bend over slightly as he walked. No jaundice was noticed.

Physical examination on January 26, 1946, revealed the liver edge to be just palpable on deep inspiration and slightly tender. The spleen was not palpable. No spider angiomas were observed. The bromsulfalein retention and plasma bilirubin were normal.

On March 25 the liver and spleen were not palpable or tender, and there were no spider angiomas.

The thymol-turbidity values were as follows on January 26, 13 units, on February 20, 11 units, and on March 25, 5 units.

CASE 5 On January 12, 1946, this 17-year-old boy developed a headache associated with chills and fever. This was followed by nausea, anorexia and an episode of vomiting. The acute symptoms lasted approximately 1 week. Other symptoms included soreness over the liver area, hives, itching of the skin, marked fatigue, somnolence, clay-colored stools and a weight loss of 12 pounds. Jaundice was noticed on January 20, 4 days after the onset of dark urine. Recovery was uneventful except for liver tenderness, which persisted for approximately 3 weeks.

Physical examination on January 25 revealed the liver to be palpable two fingerbreadths below the costal margin and definitely tender. The spleen was not palpable. A definite spider angioma was noted over the anterior portion of the neck.

On March 25 the liver was not palpable or tender, and the spleen was not palpable. The spider angioma had almost disappeared but could still be found. On August 8 the spider angioma had completely disappeared.

The liver-function tests were as follows:

DATE	PLASMA BILIRUBIN	BROMSULFALGIN RETENTION AT 45 MINUTES	THYMOL TURBIDITY
	mg /100 cc	%	units
January 26	2.8	27.5	14
February 1	1.1	3.5	17
March 25	0.8	2.0	8
August 8	0.7	3.0	5

CASE 6 On January 20, 1946, this 12-year-old boy developed a slight loss of appetite and a feeling of malaise. Two days later jaundice was noticed, and he was admitted to the hospital. The jaundice was slight and rapidly disappeared. The liver and spleen were never palpable or tender, and no spider angiomas were observed. The patient made an uneventful recovery.

The liver-function tests were as follows:

DATE	PLASMA BILIRUBIN	BROMSULFALGIN RETENTION AT 45 MINUTES	THYMOL TURBIDITY
	mg /100 cc	%	units
January 24	3.5	46	14
January 30	3.0	37	19
February 6	0.9	6	18
February 17	0.6	3	10
April 23	—	—	3

CASE 7 On January 21, 1946, this 20-year-old girl developed nausea and anorexia associated with a mild fever. This was followed by moderate abdominal pain and a feeling of fatigue. Jaundice was noticed on January 25, and she was admitted to the hospital.

Physical examination disclosed marked liver tenderness, the liver was palpable three fingerbreadths below the costal margin. The spleen was also palpable. No spider angiomas were observed. The patient showed rapid improvement on

bed-rest therapy. The liver tenderness persisted for 2 weeks after admission. Recovery was uneventful.

The liver-function tests were as follows:

DATE	PLASMA BILIRUBIN	BROMSULFALGIN RETENTION AT 45 MINUTES	THYMOL TURBIDITY
	mg /100 cc	%	units
January 25	5.0	48	17
January 29	7.0	40	28
February 5	1.4	6.0	20
February 11	0.8	2.0	21.5
February 19	0.6	1.0	12.3
February 26	0.4	2.0	9.5
March 6	0.5	1.0	6.7
March 13	0.5	1.0	6.3
April 7	0.4	1.0	5.9
April 23	0.2	2.0	4.0

CASE 8 On January 24, 1946, the mother noticed that this 3-year-old girl had lost her appetite. The temperature was 101°F. On the following day the patient was seen at the hospital.

Physical examination revealed no evidence of jaundice. The liver and spleen were not palpable or tender. The temperature was 100°F. The patient regained her appetite 2 days later, and no further signs or symptoms were demonstrable.

The liver-function tests were as follows:

DATE	PLASMA BILIRUBIN	BROMSULFALGIN RETENTION AT 45 MINUTES	THYMOL TURBIDITY
	mg /100 cc	%	units
January 25	0.5	13.5	9.0
February 2	0.2	1.0	13.0
March 25	0.3	2.0	7.0
August 8	0.4	2.0	4.0

CASE 9 On February 8, 1946, this 13-year-old boy noticed a slightly sore throat. His mother found the temperature to be 104°F. The patient had a slight headache and a decrease in his appetite at this time but no nausea or vomiting. He was admitted to the hospital 24 hours after the onset of symptoms.

Physical examination showed that the liver and spleen were not palpable or tender. There were no spider angiomas and no icterus. The throat was somewhat reddened. A throat culture was negative. The temperature was 103°F but fell to normal 12 hours after admission. Anorexia persisted for 2 days. The liver and spleen never became palpable or tender. On February 10 the patient developed a large spider angioma on the right side of the neck that had not been present on admission and another small one over the right shoulder. These showed gradual fading over a 4-month period of observation. Careful observation also revealed a slight yellowing to the sclerae on February 15, which disappeared rapidly. Recovery was uneventful.

The liver-function tests were as follows:

DATE	PLASMA BILIRUBIN	BROMSULFALGIN RETENTION AT 45 MINUTES	THYMOL TURBIDITY	CEPHALIN FLOCCULATION
	mg /100 cc	%	units	
January 26	0.4	2.5	0.5	0
February 8	0.6	30.5	3.5	++
February 11	1.0	31.5	12.5	++
February 13	2.3	34.5	16.3	++
February 18	1.3	11.5	21.5	++
February 25	0.5	3.0	22.7	+++
March 5	0.6	1.2	15.5	++
March 12	0.4	2.0	13.5	++
March 26	0.35	1.5	7.0	0

EPIDEMIOLOGY

The origin of the outbreak was not completely certain. One member of the family (M. G.) had been stationed at a naval base in Virginia at a time when a number of cases of infectious hepatitis were occurring. Approximately a month prior to the first case in the family, he came home on five days' leave. During that time he became ill with symptoms of nausea, dizziness and fever, he remained in bed at home for three days. No jaundice was noticed by

his mother, and he returned to duty at the end of his visit feeling well. No further information could be obtained. In the light of later developments, it seems possible that he had a light attack of infectious hepatitis and transmitted it to other members of the family. No known cases of jaundice had occurred in the community in recent years prior to the first case in this family.

The sequence of events may best be followed by a division of the outbreak into six parts (Fig 1). In

tenement house. This consisted of a kitchen and bedroom connected by a hallway that was broken up into three small bedrooms (Fig 2). A small bathroom and toilet opened into the kitchen. The most striking feature of the apartment was the close proximity of the seven beds in the hallway and bedroom. Two children slept in each of four of the beds, and there was considerable variation in occupancy. The father worked at night and slept during the day in any bed that was not occupied when he returned

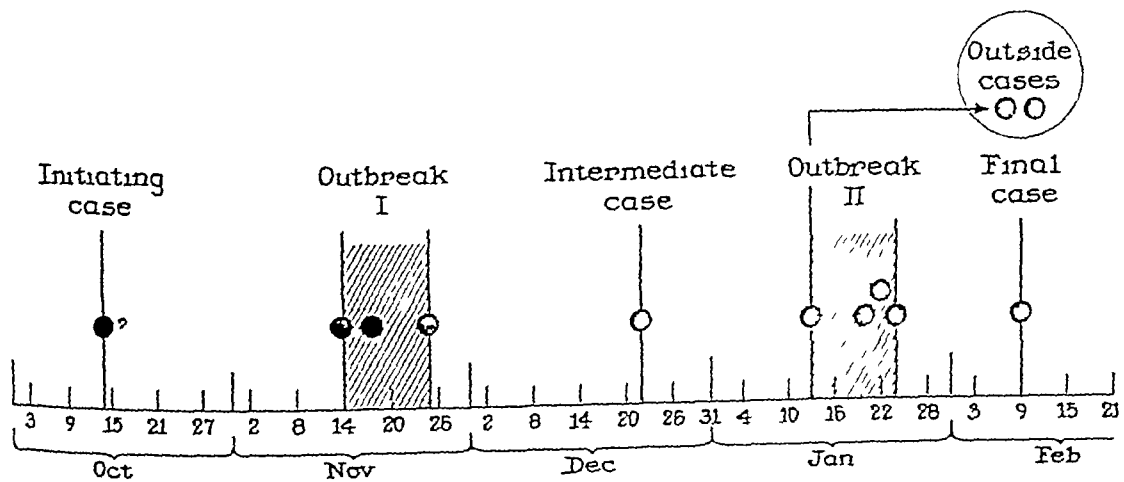


FIGURE 1 Time Relation of the Cases of Infectious Hepatitis in the Family G Epidemic

October M G, who was probably the origin of the epidemic, became ill at home while on leave from the Navy. In November, 3 siblings became ill. A month later a single case occurred in the family. In January, 4 new cases appeared in the family. And in February a single case occurred in the family and 2 cases appeared in friends of E G (Case 5).

This epidemic was not investigated until the beginning of the second outbreak in the family. The diagnosis of infectious hepatitis in the cases of the first outbreak was made on the basis of a characteristic symptomatology corroborated by at least one persistent finding, such as liver tenderness, spider angiomas or abnormalities in liver-function tests. In the other cases, which were followed throughout the course of the disease, the diagnosis was definite because of the presence of jaundice or marked aberrations in two or more liver-function tests. Six patients in the family did not show jaundice. Only 1 child and the parents demonstrated no evidence of the disease, although they were examined and tested on several occasions. This epidemic, therefore, represented 9 cases of infectious hepatitis among the children of the family and 2 cases among friends of one of the children.

The home conditions were inadequate for such a large family. The 10 children and their parents lived in a moderately small apartment in an East Side

tenement house. The sheets on the beds were changed every two weeks. Except for the crowded condition of the beds, conditions in the apartment were good. The children were kept clean, and the mother was careful with the food. The family was healthy, and no illnesses besides the usual childhood diseases had ever appeared.

Several epidemiologic studies on infectious hepatitis have been reported in which the spread of the disease was related to contact in sleeping quarters.¹²⁻¹⁵ In the outbreak under study, it is difficult to escape the conclusion that the crowded sleeping quarters were in some way responsible for the high incidence of cases.

An approximation of the length of the incubation period of the disease in this epidemic can be gathered from the fact that two friends of one patient (Case 5) developed the disease twenty-six and twenty-eight days respectively after he became ill. These friends had had no contact with any other members of the family and had not been near any other known cases of infectious hepatitis. They saw the patient only at a boys' club to which none of the other members of the family belonged, their contact was fairly close, and they admitted the possibility of an interchange of a single cigarette while the three of them together with several others, played pool. The patient attended the club during the night prior to the onset

of symptoms and then stayed away for two weeks because of illness, twenty-seven days is therefore the probable incubation period, although the possibility exists that he may have infected them several days prior to the onset of his own illness. The close relation in the time of occurrence in these 2 cases adds validity to the assumption of such an incubation period.

The 10 children of the family who were at home lived under conditions that required the closest contact. They all ate together around a very small

table to contract the disease from the 3 children with whom they lived every day during their illness in the November outbreak.

In January, 4 children developed infectious hepatitis over a period of twelve days — approximately a month after the single case in December. They must have contracted the disease from this patient who kept the infection alive in the family between the November and January outbreaks.

Finally, in February, another boy became ill with the disease. He must have obtained the virus from

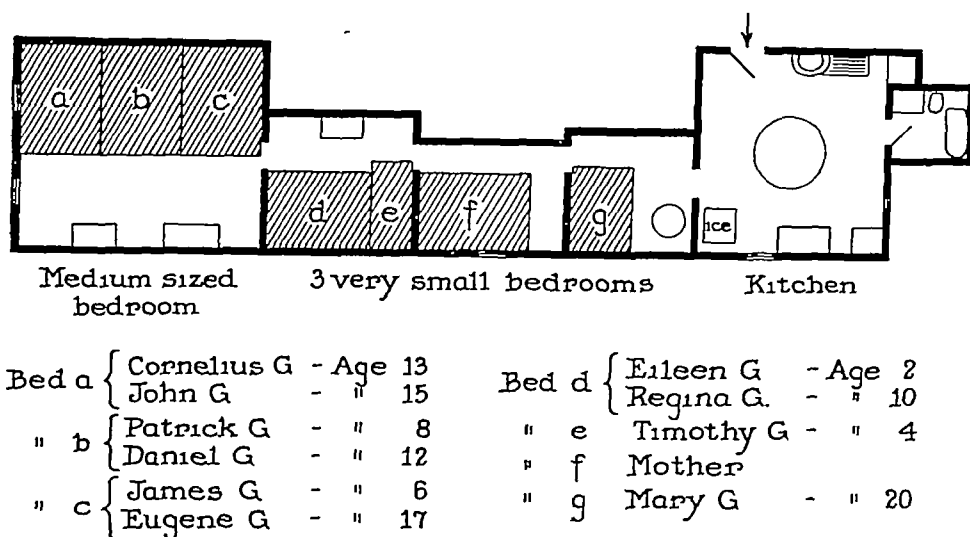


FIGURE 2 Plan of the Apartment of Family G

table, they all used the same small bathroom, and, under the crowded conditions that existed in the apartment, they practically all slept together. The older children washed and cared for the younger ones. It is to be expected that a contagious infection would spread with ease and rapidity through such a group. At least 9 of the children were susceptible to the disease, as shown by the fact that they eventually became ill. The infection, however, did not spread rapidly through the family. Three children became ill over a period of ten days in November. They probably contracted the disease from their sailor brother, who had been ill at home approximately a month earlier. Six susceptible children failed to develop the disease at that time, although they were in equally close contact with him.

In December, 29 days after the last case of the November outbreak, one boy developed the disease. He must have contracted the infection from one of the children of the November outbreak, if the incubation period is at all close to the estimated twenty-seven days. Five susceptible children failed

one of the January group after escaping three previous periods when others in his family had become infected.

One of the children apparently never contracted the disease, although he was exposed fully as much as the others in his family. The possibility remains however, that he had a subclinical infection.

The question why the parents did not come down with infectious hepatitis is a slightly different one. They were exposed to the virus in each of the outbreaks fully as much as the children. Neither gave a past history of jaundice. If they were as susceptible as the children, the chances would have been 100% that at least one of them would contract the disease. The lack of susceptibility to the disease of older people has frequently been noted. Immunity as a result of mild unnoticed infection with the disease earlier in life has been offered as a possible explanation.

This serial spread in families has been noted by Pickles² and Newman³ and is without counterpart in any other disease. That infectious hepatitis is not

extremely contagious is evident from this type of spread. The demonstration of subclinical infections, missed infections and carrier states adds strength to the idea that the disease is usually spread by contact. In the outbreak under consideration, only 5 of the 11 patients showed jaundice. Diagnosis of infectious hepatitis in 2 cases was made by means of liver-function tests alone in the absence of signs or symptoms characteristic of the disease, these are discussed below. There was definite evidence of the existence of cases that might have been missed under ordinary conditions. The chain of events in the

LIVER-FUNCTION TESTS

Following a study of various tests of liver function in acute hepatitis among Navy personnel at the Rockefeller Hospital, the conclusion was reached that the condition of the patient could best be evaluated by the determination of the plasma bilirubin, the bromsulfalein retention and the thymol turbidity.¹⁶ The use of these tests in the epidemic described above offered further information regarding their comparative significance and showed their value in the detection of cases without

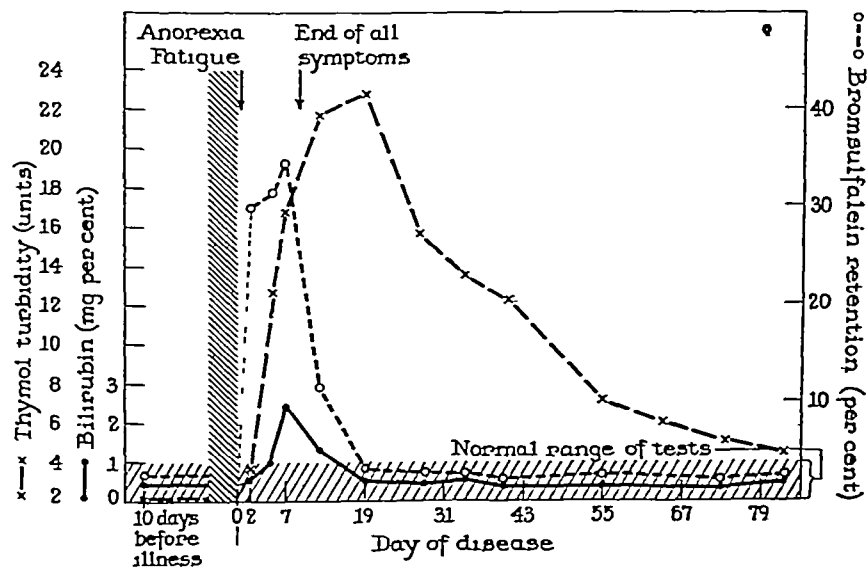


FIGURE 3 Comparative Results on Serial Determinations of Plasma Bromsulfalein Retention, Plasma Bilirubin and the Thymol Turbidity Reaction of the Serum in Cornelius G (Case 9)

epidemic would not have been evident if sole reliance had been placed on the presence of jaundice. Recent studies on poliomyelitis have shown the presence of virus in the stools of people who have had close contact with the disease and who never showed evidence of infection. They undoubtedly act as carriers. This state of affairs has not as yet been demonstrated in infectious hepatitis, although the virus is present in the feces of certain patients suffering from the disease. One cannot help remarking that the epidemiology of the two diseases has many similarities. In the family under discussion the contact between the children was extremely close, and spread by fecal contamination seems likely. Mild cases of infectious hepatitis other than those found in this epidemic must exist, and these, together with probable carriers of the virus, may explain the apparent absence of contact between cases that has often been noted and used as an argument against contact as a significant agent in the spread of the disease.

jaundice. The thymol-turbidity test was found to have special use in the epidemiologic study. Figure 3 presents the results of serial determinations in Case 9. Because of illness in his siblings, this patient was examined ten days prior to the onset of his own illness, and normal values for the various liver-function tests were found. This gave added significance to the changes produced when the disease began. It can be seen that the bromsulfalein retention became elevated within twenty-four hours after the onset of the first symptoms. Values for the plasma bilirubin did not begin to rise until the fifth day, reaching a peak on the seventh day of the disease. This peak corresponded with that of the bromsulfalein retention, and values for the two tests rapidly returned to the normal range. The curve of serial determination of the thymol-turbidity test, however, showed a delayed rise reaching a peak on the nineteenth day of the disease at a time when the other two tests had fallen to normal and the patient was free of symptoms. The thymol-turbidity values

then fell slowly, reaching the normal range on approximately the nineteenth day of the disease.

The other cases in the family that were studied also bore out the findings that the bromsulfalein retention demonstrates an immediate increase with the onset of symptoms during the preicteric stage and that the thymol-turbidity values show a delayed rise and prolonged elevation persisting well after the end of all symptoms of the disease.

Despite these marked abnormalities in liver-function tests the patient in Case 9 had only minor symptoms, consisting of mild anorexia, sore throat and slight fatigue. No definite jaundice was ever visible, and it was only by extremely careful observation that a slight yellow tinge was observed in the scleras on one day. There were none of the signs or symptoms diagnostic of infectious hepatitis. This case would have been missed if the sensitive liver-function tests described above had not been applied.

The value of these tests as diagnostic aids was also demonstrated in Case 8. This three-year-old girl developed a loss of appetite, which was reported by her mother only because the slightest signs of illness were looked for following the illness of several of the other children. On the following day the bromsulfalein test showed 12.5 per cent retention of the dye, and the thymol-turbidity value was 9 units. Subsequently, the thymol-turbidity values rose to a peak of 13 units and then slowly fell to normal, and the bromsulfalein retention remained within the normal range. The patient developed no further symptoms, the liver was never palpable or tender, and there was no jaundice or elevation of the plasma bilirubin. The pattern in this case was similar to that in Case 9, with an immediate rise and rapid fall of the bromsulfalein retention associated with a delayed rise and prolonged elevation of the thymol reactivity of the serum. The combination of these tests made possible the diagnosis of an extremely mild case of infectious hepatitis.

Several members of the family were seen just after the symptoms of infectious hepatitis had subsided, when the plasma bilirubin and bromsulfalein retention were normal. The thymol-turbidity test, however, still revealed elevated values that fell slowly to normal over a period of several weeks. The use of this test made it possible to confirm the diagnosis of infectious hepatitis after the patients had apparently recovered from the disease. The patient in Case 3 illustrates this point. He developed nausea, anorexia, pain over the liver area and diarrhea lasting for three days. Moderate fatigue and liver pain persisted for several weeks. No jaundice was noted. When he was first seen two months after the onset, he had no complaints, and physical examination was negative. Determinations of plasma bilirubin and bromsulfalein retention were normal. The thymol reactivity of the serum was still positive at 11 units, and this gradually fell to 4 over a period of several months. The symptoms of the acute at-

tack were characteristic of infectious hepatitis, and the thymol-turbidity test confirmed the diagnosis. Thus, it can be seen that this test is of value in an epidemiologic study not only because of its aid in the diagnosis of nonicteric cases but also because it remains positive for such a long period, revealing significant data after other evidences of the disease have disappeared.

OCCURRENCE OF SPIDER ANGIOMAS

Spider angiomas in the acute stage of infectious hepatitis have occasionally been described,^{17, 18} but little emphasis has been placed on their occurrence. Most clinical descriptions of the disease do not even list them among the physical signs. In a clinical study of Navy patients at the Rockefeller Hospital, approximately 30 per cent developed spider angiomas during the acute stage of the disease.¹⁹ The incidence was much higher among patients with chronic hepatitis, and new spider angiomas usually signified a poor prognosis when they developed after the acute stage of the disease. They have served as a useful physical sign for following the transition from acute to chronic infectious hepatitis.

In the epidemic under discussion 5 children showed definite spider angiomas, and their presence aided in confirming the diagnosis of the disease in some of the cases without jaundice. Case 9 offered a good opportunity to study the formation and disappearance of the angiomas. The patient was examined ten days before the illness, and a search was made for spider angiomas because of their presence in his siblings; none were found. Twenty hours after the onset of the first symptoms he was again examined, and none were found. On the following day, however, he was discovered to have developed during the night a large angioma located over the lower right side of the neck and a considerably smaller one on the right shoulder, both blanched readily on pressure. They were carefully observed for a six-month period, during which a gradual fading took place. During the second month the quality of blanching on pressure disappeared. At the end of six months, the smaller one had completely disappeared, and the larger was visible only as a small, barely discernible, red speck. These marks, however, could still be identified as spider angiomas at the end of four months, long after the illness had terminated.

In Case 3 seven definite spider angiomas developed over the arms and shoulders. The mother noticed their appearance at the time of the acute symptoms, and the angiomas were still present when the patient was first seen in the clinic two months later. They stood out more plainly against the background of his smooth, white skin than they would have in an adult. These spider angiomas faded slowly, and two could still be identified at the end of eight months, although the patient had no persistence of signs or

symptoms of the disease. Their presence confirmed the diagnosis of infectious hepatitis.

Next to liver tenderness spider angiomas proved to be the most useful physical sign in the study of the cases in this epidemic. They were of special value in the patients whose illnesses had begun before the investigation and in whom the diagnosis was not definite from the description of the acute symptoms. Their long persistence following a short, mild attack of infectious hepatitis was somewhat unexpected. It suggests the possibility that the so-called "spontaneous spider angiomas" in normal persons occasionally result from a mild attack of infectious hepatitis without jaundice. In this group of children 4 of the 5 cases showing spider angiomas were so mild that jaundice was not seen. Another point that should be raised is that the persistence of the angiomas could not be explained on the basis of a lingering hepatitis. These children all recovered rapidly and uneventfully from the acute attack. The significance of persistent spider angiomas in chronic hepatitis and cirrhosis should be evaluated in the light of these findings.

INCIDENCE OF INFECTIOUS HEPATITIS WITHOUT JAUNDICE

The existence of nonicteric cases of infectious hepatitis is now clearly recognized, but there is no agreement about the number of such cases. Various estimates for the percentage of nonicteric cases have been given: 9 per cent (Bates²⁰), 50 per cent (Barker et al.²¹), 27 per cent (Neefe and Stokes⁸), 22 per cent (Hardy and Feemster²²), and 89 per cent (Gowen²³). Undoubtedly, the percentages vary with the epidemics. A possible reason for the marked divergence noted is that each group of patients was studied in a different manner. The high incidence obtained by Gowen²³ in Tunisia is due to the fact that he estimated the icteric index in a large number of persons and considered an abnormal value as in-

The mildest case occurred in Case 8, in which the patient was the youngest of the family, and the severest case occurred in the oldest patient (Case 7). Table 1 presents the age distribution in relation to the occurrence of jaundice, and it is evident that jaundice occurred more frequently in the older age group.

SUMMARY

The serial occurrence over a period of five months of 9 cases of infectious hepatitis in a single family is described.

Contact was found to be the probable mode of spread in this outbreak.

Determinations of bromsulfalein retention and thymol reactivity of the serum proved to be valuable aids in the detection of nonicteric cases.

The thymol-turbidity test, because of its prolonged elevation, was of special value in an epidemiologic study.

Spider angiomas, which developed during the acute attack of infectious hepatitis, were found in 5 cases. The sudden onset and delayed disappearance of this physical sign are described. It proved to be helpful in corroborating the diagnosis in 2 cases.

Six children did not develop clinical evidence of jaundice.

The severity of the illness and the presence of jaundice showed a definite relation to the age of the children, the disease being milder in the younger group.

REFERENCES

1. Ford J. C. Infective hepatitis: 300 cases in outer London borough. *Lancet* 1:675-678, 1943.
2. Pickles W. N. Epidemic catarrhal jaundice. *Lancet* 1:893-895, 1939.
3. Newman J. L. Infective hepatitis: history of outbreak in Lavant Valley. *Brit M J* 1:61-65, 1942.
4. Probert S. A. Infective hepatitis. *Brit M J* 1:197, 1942.
5. Oliphant J. W. Jaundice following administration of human serum. *Bull New York Acad Med* 20:429-435, 1944.
6. MacCallum F. O. and Bradley R. Transmission of infective hepatitis to human volunteers. *Lancet* 2:228, 1944.
7. Paul J. R. Havens, W. P. Jr., Sabin, A. B. and Philip C. B. Transmission experiments in serum jaundice and infectious hepatitis. *J A M A* 128:911-915, 1945.
8. Neefe, J. R., and Stokes J. Jr. Epidemic of infectious hepatitis apparently due to water borne agent. *J A M A* 128:1053-1065, 1945.
9. Fraser R. Study of epidemic catarrhal jaundice. *Canad Pub Health J* 22:396-411, 1931.
10. Hallgren, R. Epidemic hepatitis in county of Vasterbotten in northern Sweden. Epidemiologic and clinical study. *Acta med Scandinav* 115:22, 1943.
11. Read M. R., Bancroft, H., Doull J. A. and Parker, R. F. Infectious hepatitis—presumably food borne outbreak. *Am J Pub Health* 36:367-370, 1946.
12. Murphy W. J., Petrie L. M. and Work, S. D. Jr. Outbreak of infectious hepatitis apparently milk borne. *Am J Pub Health* 36:169-173, 1946.
13. Gauld, R. L. Epidemiological field studies of infectious hepatitis in Mediterranean Theater of Operations. *Am J Hyg* 43:248-313, 1946.
14. Cullinan, E. R. Field report to British War Office, 1943.
15. Sheehan H. L. Epidemiology of infective hepatitis. *Lancet* 2:8-11, 1944.
16. Shank R. A., Binkley O. F., and Hoagland C. L. Unpublished data.
17. Turner, R. H., Snavely J. R., Grossman E. B., Buchman, R. N., and Foster S. O. Some clinical studies of acute hepatitis occurring in soldiers after inoculation with yellow fever vaccine, with especial consideration of severe attacks. *Ann Int Med* 20:193-216, 1944.
18. Bean W. B. Cutaneous arterial spider survey. *Medicine* 24:243-331, 1945.
19. Leiby D. H., Kunkel H. G., Shank R. A. and Hoagland C. L. Unpublished data.
20. Bates R. Non-sporozoa infectious jaundice. *Brit M J* 1:521-524, 1936.
21. Barker M. H., Capps R. B., and Allen, F. W. Acute infectious hepatitis in Mediterranean theater including acute hepatitis without jaundice. *J A M A* 128:997-1003, 1945.
22. Hardy H. L. and Feemster R. Infectious hepatitis in Massachusetts with review of present knowledge of disease. *Ann Ent J Med* 235:147-157, 1946.
23. Gowen G. H. Epidemiology of epidemic hepatitis. *Bull U S Army M Dept* 84:41-50, 1945.

TABLE 1 Relation of Age to the Occurrence of Jaundice

CASE NO	AGE	JAUNDICE
7	37	++++
5	20	++++
17	17	++++
4	15	0
9	13	0
6	12	++
1	10	0
2	8	0
3	6	0
8	3	0

dicative of a case of infectious hepatitis. The lack of corroborative evidence opens his findings to some question. In the family epidemic reported above 6 children had infectious hepatitis without jaundice—an incidence of 66 per cent.

Age seemed to be an important factor in the determination of the severity of the illness and the presence of jaundice in the members of this family.

then fell slowly, reaching the normal range on approximately the nineteenth day of the disease

The other cases in the family that were studied also bore out the findings that the bromsulfalein retention demonstrates an immediate increase with the onset of symptoms during the preicteric stage and that the thymol-turbidity values show a delayed rise and prolonged elevation persisting well after the end of all symptoms of the disease

Despite these marked abnormalities in liver-function tests the patient in Case 9 had only minor symptoms, consisting of mild anorexia, sore throat and slight fatigue. No definite jaundice was ever visible, and it was only by extremely careful observation that a slight yellow tinge was observed in the scleras on one day. There were none of the signs or symptoms diagnostic of infectious hepatitis. This case would have been missed if the sensitive liver-function tests described above had not been applied.

The value of these tests as diagnostic aids was also demonstrated in Case 8. This three-year-old girl developed a loss of appetite, which was reported by her mother only because the slightest signs of illness were looked for following the illness of several of the other children. On the following day the bromsulfalein test showed 12.5 per cent retention of the dye, and the thymol-turbidity value was 9 units. Subsequently, the thymol-turbidity values rose to a peak of 13 units and then slowly fell to normal, and the bromsulfalein retention remained within the normal range. The patient developed no further symptoms, the liver was never palpable or tender, and there was no jaundice or elevation of the plasma bilirubin. The pattern in this case was similar to that in Case 9, with an immediate rise and rapid fall of the bromsulfalein retention associated with a delayed rise and prolonged elevation of the thymol reactivity of the serum. The combination of these tests made possible the diagnosis of an extremely mild case of infectious hepatitis.

Several members of the family were seen just after the symptoms of infectious hepatitis had subsided, when the plasma bilirubin and bromsulfalein retention were normal. The thymol-turbidity test, however, still revealed elevated values that fell slowly to normal over a period of several weeks. The use of this test made it possible to confirm the diagnosis of infectious hepatitis after the patients had apparently recovered from the disease. The patient in Case 3 illustrates this point. He developed nausea, anorexia, pain over the liver area and diarrhea lasting for three days. Moderate fatigue and liver pain persisted for several weeks. No jaundice was noted. When he was first seen two months after the onset, he had no complaints, and physical examination was negative. Determinations of plasma bilirubin and bromsulfalein retention were normal. The thymol reactivity of the serum was still positive at 11 units, and this gradually fell to 4 over a period of several months. The symptoms of the acute at-

tack were characteristic of infectious hepatitis, and the thymol-turbidity test confirmed the diagnosis. Thus, it can be seen that this test is of value in an epidemiologic study not only because of its aid in the diagnosis of nonicteric cases but also because it remains positive for such a long period, revealing significant data after other evidences of the disease have disappeared.

OCCURRENCE OF SPIDER ANGIOMAS

Spider angiomas in the acute stage of infectious hepatitis have occasionally been described,^{17, 18} but little emphasis has been placed on their occurrence. Most clinical descriptions of the disease do not even list them among the physical signs. In a clinical study of Navy patients at the Rockefeller Hospital, approximately 30 per cent developed spider angiomas during the acute stage of the disease.¹⁹ The incidence was much higher among patients with chronic hepatitis, and new spider angiomas usually signified a poor prognosis when they developed after the acute stage of the disease. They have served as a useful physical sign for following the transition from acute to chronic infectious hepatitis.

In the epidemic under discussion 5 children showed definite spider angiomas, and their presence aided in confirming the diagnosis of the disease in some of the cases without jaundice. Case 9 offered a good opportunity to study the formation and disappearance of the angiomas. The patient was examined ten days before the illness, and a search was made for spider angiomas because of their presence in his siblings, none were found. Twenty hours after the onset of the first symptoms he was again examined, and none were found. On the following day, however, he was discovered to have developed during the night a large angioma located over the lower right side of the neck and a considerably smaller one on the right shoulder, both blanched readily on pressure. They were carefully observed for a six-month period, during which a gradual fading took place. During the second month the quality of blanching on pressure disappeared. At the end of six months, the smaller one had completely disappeared, and the larger was visible only as a small, barely discernible, red speck. These marks, however, could still be identified as spider angiomas at the end of four months, long after the illness had terminated.

In Case 3 seven definite spider angiomas developed over the arms and shoulders. The mother noticed their appearance at the time of the acute symptoms, and the angiomas were still present when the patient was first seen in the clinic two months later. They stood out more plainly against the background of his smooth, white skin than they would have in an adult. These spider angiomas faded slowly, and two could still be identified at the end of eight months, although the patient had no persistence of signs or

meat-free diet, and the patient was asymptomatic. Further x-ray studies of the esophagus, stomach and small bowel revealed no abnormality.

DISCUSSION

The possible relation of the bleeding to the exposure to low pressure is interesting. The character of the bleeding was such that it resembled a slow oozing over a period of nearly a week — it was not the sudden rush and exsanguination typical of a bleeding ulcer. It could be said that the relation of this bleeding to the exposure to low pressure was purely fortuitous. The short time between the two events is a persuasive reason for believing that the bleeding was the result of the exposure to the low pressure. In addition, the association of the abnormally severe crampy abdominal pains with the exposure to low pressure is another reason for considering the bleeding related to the latter event. The patient had had an uneventful simulated flight nine months previously to 39,000 feet for thirty minutes. Ordinarily, some abdominal distention and slight abdominal cramps can be expected on exposure to low pressure, but the symptoms were severer and associated with an inability to pass flatus, which ordinarily relieves the mild abdominal distress.

Gas saturated with moisture and at a constant temperature can be calculated to expand about six and a half times under the conditions that the patient experienced. Because of the reduction in the partial pressure of oxygen, the breathing of 100 per cent oxygen at 33,700 feet is comparable to the breathing of air at sea level. At 41,000 feet, in spite of the breathing of 100 per cent oxygen, experiments at the Aeromedical Laboratory at Wright Field showed that the blood is approximately 85 per cent saturated with oxygen. This slight anoxic state may be enough to increase the effects of any trauma to capillary blood vessels.

During the course of the war, many men were processed in low-pressure chambers. The Air Surgeon's Office reports that 470,592 simulated altitude flights were made, ordinarily including 3 flights per person, and that during the course of the flights only 6 fatal cases traceable to this experience occurred.¹

It is not the intent of this paper to discuss the reasons for these fatalities. But a brief review of the autopsy protocols in 2 cases may be of interest. The subjects showed pulmonary edema, which appeared on the average about four hours after exposure and was the immediate cause of death. None of the patients gave a history of allergy. Two patients showed gross and microscopical hemorrhage into the gastrointestinal tract.

CASE 4. This officer had been exposed to a simulated altitude of 30,000 feet for 1 hour. Post-mortem examination showed the serous surface of the entire gastrointestinal tract to be smooth and free of exudate. The serosal vessels appeared congested. No subserosal hemorrhages were seen. The stomach contained about 200 cc of brownish fluid. Scat-

tered over the mucosa of the stomach and duodenum were numerous areas of hemorrhage. These were dark red and appeared to be of recent origin. They measured from 0.3 to 3 cm in diameter. The first 90 cm of the jejunum appeared normal. The mucosa of the remaining portion of the jejunum and all except the terminal 60 cm of ileum showed what appeared to be a diffuse confluent hemorrhagic necrosis. The mucosa was dark red. The lumen of the small intestine contained a moderate amount of reddish-black fluid. The small and large intestines were not distended. The mucosa of the colon showed no lesions. The lumen of the colon contained a moderate amount of yellow, soft fecal material. The appendix was not abnormal.

Microscopical examination revealed marked mucosal hemorrhage of the stomach and small intestine. The mucosa of the stomach showed slight autolytic changes, no other pathologic changes were noted. The mucosa of the duodenum had undergone slight autolysis. A section of mucosa from the small intestine disclosed some autolytic changes. One section from the site of hemorrhage showed the villi to be hemorrhagic, and blood cells were scattered throughout the connective tissue. The mucosa was covered with material consisting of red cells. The mucosa of the colon was intact, and only minimal pathologic changes were seen.

The anatomic diagnoses were acute pulmonary edema, pleural effusion and extensive capillary damage to the mucosa of the stomach and small intestine.

CASE 5. A private had been exposed to an altitude of 30,000 feet for 30 minutes. Post-mortem examination revealed no abnormalities in the stomach. The small bowel showed prominence of Peyer's patches in the vicinity of the ileocecal valve and 45 cm proximal to it. Scattered hemorrhagic streaks were observed throughout the small bowel, especially in the duodenum and the jejunal area.

The anatomic diagnoses were laceration of the dura and herniation of the brain (left parietal lobe), with congestion and edema of the brain tissues, marked pulmonary edema and extensive congestion of both lungs and scattered hemorrhages in the small intestine.

Two possibilities exist to explain the hemorrhages. The first is that the morphologic changes were a result of the profound shock that accompanied the fatal cases. Erlanger and his associates² and later Moon³ described the distinctive circulatory changes in shock that correspond to the gross and microscopical picture presented in these fatal cases.

The second possibility, which is theoretically plausible, is that air emboli developed in the distended capillary network of the bowel where the circulation was impeded. The mechanical distention from the formation of air emboli caused disruption and increased permeability of the capillary endothelium. It does not seem likely that the slight systemic anoxia, which was undoubtedly present in the case presented above, was in itself sufficient to cause hemorrhage, but conditions in the bowel may have aggravated the local anoxia that was present.

This first possibility may well apply to the fatal cases but not to the case reported above, for at no time did the patient give evidence of being in shock. It can safely be assumed that the bleeding in that patient was below the level of the pylorus, for it is infrequent that a gastric lesion is not associated with hematemesis.

Inquiries addressed to the Committee on Medical Research of the Office of Scientific Research and Development led to a reply from Dr. Kenneth B. Turner,⁴ chief of the Record Section, who did not recall having heard of a previous example of mas-

MASSIVE GASTROINTESTINAL BLEEDING FOLLOWING EXPOSURE TO LOW PRESSURE

W WILSON SCHIER, M D *

BOSTON

IN recent years reports of gastrointestinal hemorrhage from obscure and comparatively rare origins have been accumulating. Hematemesis is an exceedingly dramatic episode for the patient, and melena is equally so for the physician. After gastric or duodenal ulcer, varicosities of the esophagus and rectum or carcinoma of the stomach and large bowel have been dismissed, a diagnostic impasse is reached. This paper is the result of such a situation. No attempt is made to present an inclusive differential diagnostic study, but the possibilities of various lesions of more infrequent occurrence are considered. McBurney has been quoted as saying, "Deliver me from the man of one case." Nevertheless, the following single case report is presented as a diagnostic problem.

CASE REPORT

On October 2, 1943, a 29-year-old medical officer was admitted to a station hospital because of bloody diarrhea of 2 days' duration.

The past history was not remarkable except for a strong family and personal history of allergy. On one occasion 4 months previously, the patient had noted several purpuric spots on the forearms preceding a flareup of chronic neurodermatitis. In 1942 a tonsillectomy and adenectomy had been done without complication. A system review was non-contributory.

Two days before admission the patient had been exposed to a simulated altitude of 41,000 feet while demonstrating some of the phenomena of high-altitude physiology. He had felt well before entering the low-pressure chamber where this demonstration had taken place and had taken no medication except for 0.25 per cent Neosynephrine nose drops to alleviate symptoms of hay fever and to prevent aero-otitis. In addition, he had drunk a bottle of Coca-Cola before entering the chamber.

In a period of 20 minutes, pressure in the chamber was reduced from that of the ground level, approximately 12 pounds per square inch, — equivalent to 4280 feet above sea level, — to 2.6 pounds per square inch — equivalent to an altitude of 41,000 feet. During the reduction in pressure, the patient had crampy abdominal pain with distention. This was mild at first but increased during the 10 minutes at that pressure. The pressure was then increased to 2.75 pounds per square inch — equivalent to an altitude of 39,000 feet. This was maintained for ½ hour. The abdominal pain was not disabling but was definitely uncomfortable. It was relieved on return to ground-level pressure, the transition occupying 15 minutes, at that time the patient felt well. The abdominal pain disappeared during the increase in pressure.

He ate a good supper and went to bed early and to sleep quickly. About 4 hours after retiring he was awakened with crampy abdominal pains that were generalized and associated with a desire to evacuate. A large bloody diarrhea containing dark clots ensued. Three hours later similar rectal bleeding occurred. The next day the patient felt well and went about his daily duties. Three more stools, however, in the next 24 hours, more formed in character but tarry, brought him to the hospital.

The chief complaint on admission was a feeling of fatigue and muscular weakness. Physical examination was negative

except for pallor of the skin, congestion of the nose and a tarry stool on rectal examination.

The temperature was 98.6°F, the pulse 92, and the blood pressure 124/78.

Examination of the blood revealed a red-cell count of 4,300,000, with a hemoglobin of 13 gm, during the day the red-cell count fell to 3,500,000, with a hemoglobin of 12 gm. (On the day before admission, the red-cell count had been 5,070,000.) The nonprotein nitrogen was 32 mg and the blood sugar 115 mg per 100 cc, and a blood Kahn test was negative. The urine was a clear amber, with a specific gravity of 1.026, negative for albumin and glucose and microscopically normal.

On the 2nd day the patient felt better in the morning. The blood pressure was 122/78, and the pulse 90, the abdomen was soft without masses or tenderness. Toward evening the abdomen became distended, and the oral temperature rose to 99.0°F, and the pulse to 142. The red-cell count was 3,080,000, with 9 gm of hemoglobin and abundant platelets. The bleeding time was 90 seconds, and the clotting time (capillary tube) 45 seconds, the tourniquet test was negative. The white-cell count was 8200, with 70 per cent segmented and 2 per cent nonsegmented neutrophils, 24 per cent lymphocytes, 2 per cent monocytes, 2 per cent basophils and no eosinophils. A transfusion of 400 cc of Type A citrated blood was given without reaction.

On the 3rd hospital day the stools were reported negative for ova and parasites and nonlactose fermenting bacteria. The abdomen was less distended, the skin was pale, and the patient was comfortable but feeling much more lassitude. The diet was a modified Meulengracht regime with feedings of puréed food every 2 hours. The appetite was poor. Amphojel and lime water were given between feedings. That evening a 600-cc transfusion was given without reaction. The temperature had been rising throughout the day and had reached 103°F before the transfusion was begun. It fell slowly to normal in the next 36 hours and was accompanied by a fall in pulse.

On the 5th hospital day the stools became normal in appearance but remained guaiac positive. The patient was given a normal diet at that time.

On October 11 a proctoscope was introduced to its full distance of 25 cm without difficulty. The mucosa of the sigmoid and rectum appeared entirely normal. There were no tumors or areas of ulceration and no bleeding points. A small internal hemorrhoid was not believed to account for the bleeding.

On October 12 preliminary fluoroscopy of the chest was entirely negative. Examination of the large bowel showed no evidence of intrinsic organic disease. The terminal ileum filled and appeared normal, the appendix was partially filled. X-ray films made with the colon filled and after the evacuation of the barium, as well as contrast films after evacuation, failed to demonstrate any lesion within the large bowel.

On the following day preliminary chest fluoroscopy was again entirely negative. The esophagus was normal. The stomach was hyperactive, with deep regular peristaltic waves and rapid gastric emptying. The duodenal cap filled out well and showed no defects and no evidence of irritability. The duodenal loop appeared normal. Serial films of the small bowel made at hourly intervals disclosed no abnormality in the distribution of the barium meal.

On October 15 the patient was placed on a meat-free diet for 48 hours. The stools gave a ++ guaiac reaction but were guaiac negative 2 days later, when the patient was discharged. Examination of the blood at that time showed a red-cell count of 4,000,000, with 12 gm of hemoglobin. The patient was given a month's sick leave before resuming his regular duties and advised to continue amphojel, to avoid strenuous exercise and to have an x-ray checkup examination on return to duty.

One month after admission careful x-ray examination of the esophagus, stomach and duodenum was negative. Eighteen months later the stools were negative for occult blood on a

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recurrent hemorrhages of unknown nature leave surgery as the only resort

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REFERENCES

1. Dwyer V. M., Office of the Air Surgeon, Headquarters Army Air Forces, Washington D. C. Personal communication.
2. Eraser J., Gesell R., Gasser H. S. and Elliott, B. L. Experimental study of surgical shock, preliminary report. *J. A. V. A.* 69: 209-2092 1917.
3. Moore V. H. *Shock and Related Capillary Perforations* 442 pp. New York: Oxford University Press, 1938.
4. Turner K. B. Technical Information Division, Army Service Forces, Office of the Surgeon General, Washington D. C. Personal communication.
5. Felton, J. F. Division of Medical Sciences, Committee on Aviation Medicine, National Research Council, Washington D. C. Personal communication.

6. Osler W. Visceral lesions of purpura and allied conditions. *Brit. M. J.* 1: 517-525 1914.
7. Stone H. B. Large melanoma of obscure origin. *Tr. Am. S. A.* 62: 582-597 1944.
8. Somerich A. and Nichols H. G. Hemorrhage from Meckel's diverticulum in adult: report of case. *New Eng. J. Med.* 228: 12-14 1943.
9. Abrams A. L. Relation of intestinal bleeding to heterotopic gastric mucosa and ulceration in Meckel's diverticulum. *J. Pediatr.* 13: 211-1938.
10. Winkelman A. Ulcer in Meckel's diverticulum. Unusual roentgenologic findings: case report. *J. Mt. Sinai Hospital* 8: 1116-1120 1942.
11. Rankin F. W. and Mayo C. 2nd. Carcinoma of small bowel. *Surg. Gynec. & Obst.* 50: 9-9, 947 1930.
12. Knudsen P. Benign neoplasms of small intestine complicated by severe hemorrhage: report of two cases, operative intervention and recovery. *J. Mt. Sinai Hosp.* 4: 972-979 1938.
13. Seegal H. L., Scott W. J. M. and Watson J. S. J. Lesions of small intestine producing massive hemorrhage with symptoms simulating peptic ulcer. *J. A. M. A.* 129: 116-120 1945.

MEDICAL PROGRESS

PEDIATRICS (Concluded)*

MEMBERS OF THE STAFFS OF THE CHILDREN'S AND INFANTS' HOSPITALS†

BOSTON

ATTITUDES TOWARD INFANT CARE

The care of infants is largely influenced by physiologic and psychiatric knowledge, much of which has accumulated in the past few years. Fundamental in this care are the notion that healthy newborn infants are physiologically equipped for survival in the environment into which they are born and, secondly, the certainty that, for the building up of a healthy new personality, a firm and comfortable relation between the infant and its mother is essential.

A suitable environment presupposes a mother or mother's substitute whose main concern is the welfare of the baby. She should be one person over a long period, since changing or competing persons make the proper emotional relation difficult. The second vital factor in the environment is food adequate in amount and suitable in quality. Protection from exposure and infection, which is also necessary, has already been discussed.

Introduced into such an environment, the baby has first of all an innate impulse to grow and develop. Growth varies tremendously in its intensity. Some well nourished babies weigh 17 or 18 pounds at the age of a year, whereas others weigh 10 pounds more at the same age. Running parallel to the impulse to grow are the senses of hunger, appetite and satiety, which govern much more accurately than any table of calories and ounces the amount of food needed and the frequency of its need. Food forced beyond the requirement indicated by instincts results in no increase in growth.

The impulse toward maturation of the nervous system is as inherent and characteristic as the growth impulse. It can be slowed only by major disasters and probably cannot be hastened by any method of training or feeding. The newborn has not the necessary intellectual equipment to learn by conditioning or teaching, and only begins to develop this faculty during the latter half of the first year. At birth, voluntary movement hardly exists, and years are required for its elaboration and perfection, the lateral tracts of the spinal cord remain only partially myelinated well into the second year. The differentiation between sleeping and waking, apart from the stimulus of hunger, is gradually developed in early infancy.

Emotional needs also tend to mature during infancy, but it appears that for an infantile emotional need to atrophy it must have been amply satisfied at some time. The most urgent infantile emotion seems to be the need for personal attachment to one person. Sucking, mouthing, smelling and feeling all appear to give a sense of emotional relaxation to infants, and many babies become irritable if deprived of them before they are outgrown. It may be that wetting and soiling are similarly satisfying in early infancy. Whether head banging, bedrocking and similar rhythmic motions are to be regarded as normal satisfactions or as evidences of pathologic emotional tensions is dubious, since such habits tend to appear in emotionally tense or defective infants.

Granted these hints regarding a point of view, what are the practical applications? So-called "demand feeding" is one of the most widely discussed issues at present. The notion is to feed the baby when he is hungry and cries for food. Such a schedule is often irregular during the first few days or weeks and is difficult to administer in the average lying-in hospital. Fortunately, most infants seem

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sive intestinal bleeding following exposure to low pressure

Dr John F. Fulton,⁵ chairman of the Subcommittee on Decompression Sickness, National Research Council, reported that he had observed no cases of gross hemorrhage following exposure to high altitudes

Causes to be considered other than anoxia and distention are a Meckel's diverticulum, allergy and primary tumor of the small intestine

In 1808 Willan in his book *Cutaneous Disease* mentioned the relation of anasarctous lesions of the thighs and hands, presumable angioneurotic edema, associated with purpura, vomiting, abdominal pain, diarrhea and bloody stools. This was described more fully by Henoch in 1874, and the symptom complex was given his name. Sir William Osler⁶ presented several cases of purpuric and sometimes merely erythematous skin lesions associated with visceral lesions, particularly gastrointestinal bleeding.

The allergic background in the case presented above makes Henoch's purpura a possibility, but the single occurrence of bleeding and the older age group make this possibility less probable. An adequate follow-up study was not possible for the full evaluation of other possibilities. Esophagoscopy and gastroscopy might have been helpful. Early x-ray films would have been desirable after this massive gastrointestinal hemorrhage, and postponement of such examination may be the reason why no lesion was found.

Cases of undiagnosed gastrointestinal bleeding are common to the experience of every doctor, but not frequent enough for generalization from his personal experience. Stone⁷ presented 72 cases of massive melena of obscure origin, in 31 of which no cause could be ascribed, 6 of these patients were subjected to celiotomy—one on two occasions—without further elucidation of the etiology. Even at post-mortem examination of subjects with cirrhosis of the liver, esophageal varices are often demonstrated only with great difficulty although death followed sudden hematemesis.

Congenital diseases must be considered as causes of intestinal bleeding. Autopsy studies reveal that Meckel's diverticulum occurs in about 2 per cent of the population and three times as often in males as in females. The diverticula often contain heterotopic gastric mucosa or pancreatic tissue that is subject to ulceration.^{8,9} The symptoms often simulate peptic ulcer both in periodicity of pain and in bleeding. X-ray films of the small intestine do not contribute definitive information, and in the presence of questionable roentgenographic findings, a presumptive diagnosis of peptic ulcer is often made. The failure of x-ray examination to outline Meckel's diverticula is probably a result of their usual structure. Typically, the orifice is relatively large with a small lumen. The diverticulum is short,

consequently, barium enters easily and leaves promptly. In addition, overlying masses of small bowel may obscure diverticula that do remain filled. In fact, x-ray visualization is considered something of an achievement.¹⁰

Primary tumors of the small intestine are rare but are frequently associated with bleeding, intussusception and pain. Rankin and Mayo¹¹ list 31 cases of small-bowel carcinoma seen during the same interval in which 2646 cases of cancer of the stomach and 2775 of the large bowel and rectum were seen. Klingenstein¹² describes 2 cases of benign lesions of the small intestine complicated by severe hemorrhage. Benign tumors occur about half as frequently as the malignant variety. Segal, Scott and Watson¹³ presented a case of carcinoma of the jejunum in which the patient exsanguinated to a hemoglobin level of 6 gm. The carcinoma was a 3-mm nodule in the center of which was an area of ulceration. In the case presented above tumor seems unlikely because bleeding has not recurred in nearly three years.

In cases of massive gastrointestinal hemorrhage treatment for the loss of blood is, of course, of paramount importance. Early x-ray study seems advisable if the roentgenologist is cautioned to avoid kneading the abdomen. Under these circumstances, there can be little objection to x-ray examination except when the possibility of intestinal obstruction is present. Esophagoscopy and gastroscopy are recommended as part of the complete examination. Blood studies to eliminate certain purpuras as etiologic factors are necessary.

Stone⁷ emphasizes the fact that premature surgery should be avoided. It is quite possible that patients who have bled only once will bleed no more. When the source of bleeding is definite, surgery is indicated. In the cases that seem completely unexplained and in which the hemorrhages are severe and recurrent, operation is the recourse of desperation and bafflement. Such intervention may fail to discover or to relieve the difficulty.

SUMMARY

A case of severe intestinal hemorrhage associated with exposure to low pressure during simulated high-altitude flight is presented. The differential diagnoses are discussed, and possible etiologic factors reviewed—namely, shock, acute dilatation and air embolism of the bowel and increased capillary permeability associated with an allergic diathesis.

Other possible sources of bleeding of an obscure nature are discussed, including Meckel's diverticulum and new growths of the small intestine.

Treatment is symptomatic, with early transfusion. After the bleeding has been controlled, diagnostic procedures can be considered. Surgery is indicated when the source of the bleeding is definite and the lesion is remediable by surgery or when severe

These illustrations are, of course, isolated items from the life history of any child. They are presented in the hope of illustrating the point of view that, given time to mature appropriately before being asked to assume various responsibilities, each child will grow up able to utilize his innate abilities. A baby so handled has the satisfaction of developing new abilities and new aptitudes as a result of his innate endowment, rather than the frustration of having them imposed on him by a system that he neither understands nor desires. Pressure to learn early, constant training and strict discipline may tend to modify these abilities in a downward direction by producing a habit of resistance, frustration and anxiety. Finally, the resilience of the human infant and child must be recognized, for many able adults appear to have been most unwisely handled in childhood.⁶⁵⁻⁶⁹

DIAGNOSIS AND MANAGEMENT OF SEIZURES

This subject is particularly pertinent for pediatricians, because the younger the animal organism (whether human or subhuman) the greater the susceptibility to seizures, whether these are "spontaneous" or induced by a convulsant drug or fever. Each year the magazine *Epilepsia* reviews approximately two hundred and fifty articles that deal with the subject of convulsions or epilepsy. Yet only two or three articles in a hundred have appeared in a journal devoted to pediatrics. The brevity of the present review emphasizes the apathy of pediatricians toward this important and interesting disease.

Differentiation of the causes of seizures calls for detailed and co-ordinated study of patients with the co-operation of geneticists, obstetricians, pathologists and social therapists and with the aid of laboratory technics, particularly the electroencephalograph. A commendable effort in this direction is the long-term study of 800 epileptic patients at the Harriet Lane Hospital in Baltimore.⁷⁰ In 10 per cent of these patients the first convulsion occurred during fever. The prognosis proved to be better when there was a family history of childhood convulsions than if there was none. A report of book length is promised of the neurologic, physiologic and social pathology disclosed by this study.⁷¹ An interesting tabulation of the incidence of convulsions in 1543 children with various pathologic conditions has been made by Crump.⁷² For example, convulsions occurred in 7 per cent of patients with extracranial infections, in 55 per cent with meningitis, in 41 per cent with brain tumor, in 39 per cent with encephalitis and in 10 per cent with head and birth injuries. Among 1330 institutionalized patients reviewed by Yannet⁷³ there were 52 essential (genetic) epileptic patients (3.9 per cent). In addition there were 190 patients (14.2 per cent) with convulsive disorders. In the latter group, cerebral palsy, trauma and infections were most important. Also,

the incidence of convulsive disorders was directly related to the severity of the mental defect. A practical and useful discussion of various aspects of epilepsy in childhood is presented by Buchanan.⁷⁴

Fresh contributions to the management of epilepsy have been limited to new anti-seizure drugs. Of these, the preparation of greatest interest to the pediatrician is one that seems to be of specific value in the control of the petit-mal triad. These attacks are frequently repeated transient blackouts, myoclonic jerks or akinetic seizures. Up to now they have resisted drug therapy. Experience has conclusively demonstrated the effectiveness of Tridione (3,5,5-trimethyl oxazolidine-2,4-dione) in controlling seizures of the triad.⁷⁵⁻⁷⁶ Contrary to the reports of others,⁷⁷⁻⁷⁸ this drug has been found to precipitate rather than to control grand-mal seizures. It also often causes photophobia, skin rashes or diminution of the white cells, particularly the neutrophils, of the blood. Two deaths from aplastic agranulocytic anemia have been reported.⁷⁹⁻⁸⁰ Monthly blood examinations of patients taking this drug should prevent repetition of these disasters.

Demonstration that Tridione seems to have a specific action on the type of seizures associated with an alternate dart and dome formation of the electroencephalogram encourages further laboratory and clinical studies.

CEREBRAL PALSY

Cerebral palsy is admittedly a frequent and serious condition. Recently, a series of articles suggested treatments with drugs, such as prostigmine⁸¹⁻⁸² and curare, and gave publicity to its educational aspects. Public interest has been excited, and medical advice is being sought by parents whose hopes are high. The urgent need at the moment seems to be not so much information on details as a sound basic philosophy.

By convention, the term "cerebral palsy" is used to describe an abnormality in children who have motor disturbance due to cerebral lesions that have been present from birth. This definition should probably be extended to include cases with onset during the early years of childhood. Obviously, a clear distinction is necessary between cases in which extensive medical study of progressive, active disease may be needed and those in which active disease does not appear to be involved. It is only the latter problems that are discussed here.

The causes of cerebral palsy, as defined above, are, of course, many. There is certainly a group that depends on heredity. Cases of this type seem to be rare and are certainly overemphasized in the literature. A second group depends on vaguely understood prenatal disease or accident to the mother.

Recent work on German measles in the early months of pregnancy has called attention to this phase of the subject, and the occurrence of cerebral palsy in children of mothers who have had bleeding

to do well enough on the usual four-hour schedule, with only one or two feedings at breast during each of the first two postnatal days. A few babies, however, seem to be comfortable only on more or irregularly spaced feedings, this is true of both breast-fed and bottle-fed children. In the course of a few weeks on such a schedule, babies tend to cut down on the number and frequency of feedings, so that five feedings a day usually suffice within a few weeks after birth. The physiologic soundness of this method is, of course, attested by the competitive success of mammals in general.

In administering such feedings it should be realized that the reaction of the baby to either overfeeding or underfeeding is much the same, crying being the outstanding symptom. The underfed baby characteristically takes feedings eagerly and hunts for more food when the supply is exhausted, whereas the overfed infant tends to oversleep the next feeding. Hunger in infancy is akin to pain, and pain unrelieved often leads to anxiety and panic. In the majority of cases this mechanism is the foundation of so-called "colic." It is certainly a fact that babies of a few days or weeks cannot be trained to do without a feeding at night or other times. If the desire for food arises, it is in no sense volitional, but is an expression of physiologic need. The sooner this need is met, the faster the baby will be able to gain and store food to allow it to sleep for longer periods, and the less panic and anxiety will have been stimulated.

The introduction of semisolid foods must wait on the development by the infant of the ability to swallow them, and feeding of starches, ability to digest them. An incompletely satisfied appetite helps the baby to want to take new foods, but a really hungry baby expects sucking to be the means to satisfaction and will usually not accept food from a spoon until after at least partially satisfied by breast or bottle, hence, semisolids are usually taken better after the bottle than before.

In the second year appetite is often greatly reduced, many babies in this age group consuming roughly half the food taken a few months previously. At that time a quart of milk a day may well fulfill the caloric needs entirely, and a mixed diet cannot be taken in addition. Drastic cutting of the size of servings — to teaspoonfuls instead of tablespoonfuls and to demitasse instead of eight-ounce cups — will usually keep the child co-operative rather than rebellious at mealtime. Following infections, similar measures may be necessary for a few weeks.

The frequency and character of stools, especially in breast-fed babies, are often far too carefully supervised. Since the stools of the breast-fed infant never become hard and bulky as those of formula-fed babies often do, there is no reason why the infant should have stools at any prescribed interval, certainly, many do well moving their bowels only once

or twice a week. On the other hand, some thriving breast-fed babies have many loose, green stools a day. Except for the housekeeping inconvenience, no harm is done, and weaning on this account is not wise.

In bottle-fed babies infrequent stools tend to become hard and may be the cause of rectal fissures, with attendant discomfort and secondary difficulty in bowel training. Proper attention to the formula or the use of a more laxative sugar will usually improve the situation.

Most of the increments of behavior acquired by infants appear by virtue of anatomic and physiologic processes of maturation. Parents know that children sit, stand, walk and talk during stages of natural development. What is not appreciated by many is that babies also give up sucking for their food as they develop — sometimes toward the end of the first year and sometimes not until well into the second year. When the infant is ready to dispense with this method of eating he readily takes to the offered cup and does not need to be "broken from the bottle." Babies so weaned appear to be less likely to suck their thumbs or fingers than those forcibly put on the cup.

Sphincter control is gained by the same process of development. It is acquired slowly in the second year, in most cases, during waking hours and often not until the third or fourth year during sleep. So-called "training" of the infant for stool during the first few months trains the mother or nurse to anticipate the time of the bowel movement and thereby saves laundry, but is of no value. Many babies so "trained," when old enough to control their stools, seem to withhold them purposely when toileted, they are often more difficult to train than those who are first trained when they can understand the process and co-operate. Most babies cannot acquire bladder control in the daytime until well enough developed to announce their needs, and for a long time after this accidents will happen. This point of view is not aimed at relieving the growing organisms of responsibility indefinitely but is oriented toward postponing it until a stage of development appropriate to its assumption has been reached.

School must likewise be regarded as basically a physiologic process of maturation on which the teacher works. Reading readiness tests and the like, given by schools, are a tacit admission by them of the fact. The child placed in the school system at a level beyond his capacity cannot take his responsibility, which for most children is the main aim of education in the long run. A child who must be kept up by extra help and who cannot afford to miss a class or a day at school is usually placed too far ahead in the school system. The temptation to get too far ahead is a strong one, for the child of five or six is so active that the mother is glad to have the school take him off her hands for part of the day at as early an age as possible.

Eosinophilic granulomatous lesions of bone have recently been described by Lichtenstein and Jaffe⁸⁸ and by Green and Farber⁸⁹ and an attempt has been made to place these lesions in their proper category among bone dyscrasias. The former authors believed that they were describing a new clinical and pathological entity, whereas the latter indicated that the lesion was related to the lipid diseases of bone, variously considered under the names of Hand-Schüller-Christian and Letterer-Siwe diseases. Regardless of the true category, the term "eosinophilic granuloma" is a useful one to bear in mind when cyst-like lesions of bone, many of which were formerly thought to be malignant and were frequently diagnosed as multiple myelomas, are being considered.

The early diagnosis and more rational treatment of slipped femoral epiphysis have recently been emphasized in an effort to prevent the severe crippling that ensues when the condition is neglected.^{90, 91} Probably no lesion of developing bone is more serious in end-result than a bilateral slipped femoral epiphysis, which produces degenerative changes in both hip joints. Any child between the ages of nine and fifteen years, particularly if obese, who complains of pain in the hip, knee or anterior thigh should be carefully evaluated, the possibility of a slipped femoral epiphysis being always borne in mind, and early x-ray films of both hip joints obtained. Early diagnosis is essential if a normal hip joint is to be maintained.

Progress in the orthopedic management of poliomyelitis centers around the introduction of the Kenny method of physiotherapy and its supposed conflict with accepted methods of treatment.⁹²⁻⁹⁴ Since varying physiotherapy technics are usually expressions of temperament and background rather than new discoveries, the introduction of a new variation would have excited little comment, were it not for the crusading fervor of its founder and the deliberate and belligerent attack on the older and less dramatic procedures in vogue. The Kenny method emphasized the value of early mobilization of paralyzed extremities by active exercises, as well as the dangers inherent in rigid and prolonged immobilization. All of this is desirable. The rest of the method might be dismissed as redundant, were it not for the unhealthy press, radio and cinema publicity, which tends to overemphasize the value of this form of physiotherapy in the convalescent management of poliomyelitis.

Acute hematogenous osteomyelitis is essentially a disease of children. Treatment has changed radically with the introduction of penicillin.^{95, 96} Therapy in children under two years of age has been conservative, but in older children, treatment in the past was mainly surgical, with incision and drainage and packing of wounds. Chronicity and prolonged invalidism usually resulted. The present management of acute osteomyelitis is to use penicil-

lin as soon as possible after onset and in large doses. The degree of bone damage is directly proportional to the time elapsing between onset and drug therapy. Of great importance is education of pediatricians to the value of early diagnosis and early medical therapy. Frequent examination of the local lesion, however, is necessary, and the indications for surgery should be well outlined. These include abscess formation and persistent and increasing pain and swelling of the affected part, in spite of adequate dosage of the drug. It is highly desirable to take a blood culture on the child before therapy is instituted, since in this manner the organism can frequently be identified and its sensitivity to penicillin determined. Penicillin therapy should be continued for at least three weeks, or longer if indicated. Surgery should always be minimal and directed toward a specific objective, such as evacuating an abscess or decompressing a bone lesion. Extensive bone stripping and packing are obsolete. Closure of the wound around rubber tubes or cannulas and instillation of penicillin solutions postoperatively lead to early healing and minimal scarring and dysfunction, and in most cases acute osteomyelitis heals without the development of chronic osteomyelitis. This type of management of acute hematogenous osteomyelitis represents a drastic departure from the older methods rather than a modification of technics.

Acute osteomyelitis in children was formerly invariably followed by prolonged suppuration and chronic bone infection. The management of chronic osteomyelitis has altered radically with the introduction of penicillin. At present, it is recognized that necrotic material must be removed surgically. Exploration of draining sinuses and sequestrectomy are still fundamental, but with parenteral drug therapy and direct instillation of penicillin into the wound through tubes, early secondary closure is possible and prolonged suppuration and spread of infection to adjacent bone may be avoided.⁹⁷

New technics have been introduced in the treatment of deformities due to unequal length of the lower extremities. Surgical procedures for lengthening shortened extremities have largely been replaced by selective ablation of the epiphyses in the longer extremity. This procedure, usually termed "epiphyseal arrest," is performed during the period of active growth, and the "timing" of the operation is determined by reference to tables that give average growth expectancy for the epiphyses at various ages. Recent studies on the effects of irradiation on epiphyseal growth may result in quantitative reduction in growth by selective roentgenotherapy of epiphyses at various ages, without recourse to surgery. This procedure is still highly experimental and dangerous, and so far not sufficiently perfected to be used clinically, but offers a promising field for the future.⁹⁸

early in pregnancy supports the theory that various unfavorable events during the early months interfere with normal cerebral development

Birth injuries are frequent, and it is extremely important to make a clear distinction between birth injury and obstetric error. The former means that the infant was damaged during the extremely complicated mechanical and chemical stresses involved in the process of delivery.⁸³ There is increasing evidence that a continuous study by obstetricians and their colleagues is throwing light on prenatal asphyxia, the choice of anesthetics, the durability of premature babies, the causes of hemorrhage of the newborn and so forth, as well as on ways to minimize structural trauma during the delivery of full-term babies. All that should be meant by birth injury, then, is that the infant did not withstand the stresses to which it was exposed.

The occurrence of erythroblastosis, with consequent injury to the nervous system, is under constant and productive investigation, and accurate forecasts and preventive measures are available.

Another group of children pass through the perils of birth and the neonatal period and, after a period of normal development, are the victims of some acute encephalopathy, with consequent motor disturbances. Lead poisoning, thrombosis of the cortical veins, subdural hematoma and the various encephalitic processes that occur with measles, whooping cough and the like are examples. Acute and active diseases must be handled by whatever surgical or medical means are available, and no attempt is made to go into this aspect of the problem.

After all evidences of active disease are over, the physician is faced by a task that can be handled in either of two ways. He can take refuge in the hoary and inadequate formula that the nervous system has only two ways of modifying motor patterns. If the anterior-horn cells are damaged, flaccidity will appear, or if any damage above the level of these cells occurs, spasticity will result. There is no validity in this conception, and it should be rejected. On the other hand, the physician can attempt to make a physiologic and psychologic appraisal, which will reveal not only the disability but also the assets of the child, and can then proceed to work out a plan of management.

If this second plan is accepted, the first thing to do is to proceed in an orderly way to determine what the activity of the child is like. From laboratory evidence it is clear that almost complete decerebration may not be inconsistent with life. From this extreme it is entirely possible to go to the most minor and transient disability.

The motor results of cortical injury are to confuse or abolish planned activity. If the basal ganglia are impaired, associated movements are disturbed, with tremor, athetosis and so forth as salient symptoms. In cases of severe diffuse lesions of the whole forebrain, tonic neck reflexes on rotation of the head

are frequently seen with consequent extension on the side to which the chin is turned and with contralateral flexion of the arm and leg.⁸⁴ Cerebellar lesions, of course, are likely to produce ataxia. It is not difficult to make a rough physiologic appraisal and to compare it with normal behavior at the appropriate age.

Since intelligence is obviously one of the elements in motor control and certainly the controlling factor in effectiveness from the social and economic point of view, an effort should be made to investigate it. Conventional psychometric examination with the result expressed as an intelligence quotient is useful but treacherous. An evaluation by a psychologist who is familiar with handicapped children is better, but even then a single test is less valid than a series at intervals of a year or so.⁸⁵

With the psychologic and physiologic data in hand, it is necessary to consider the effect of the disability in terms of growth and development. At some point it may seem wise to use some of the specialized technics, such as pneumoencephalography and electroencephalography, to obtain a picture of the anatomic and physiologic status of the brain.

Neurosurgical treatment seeks to achieve functional balance by subtraction. If a subtracting technic, such as nerve section, is proposed, it appears reasonable to demand that the family be acquainted with the available physiologic capital from which subtraction is suggested. In the same way, if elaborate and prolonged training procedures are advised, some definite idea of the aim of the procedures should be mapped out.⁸⁶ At the moment it seems clear that many patients are being ingeniously treated as children, without any distinct notion of the ultimate results in terms of adult competitive activities.

The numerous organizations that are dealing with the disabilities of children will be wise if they face resolutely the disconcerting fact that the average child suffering from cerebral palsy comes to adult life unprepared for the competitive world that may be too much for him. The test of successful guidance during childhood comes at adolescence or in early adult life. So far, the results have not been good.

ORTHOPEDIC SURGERY

A new method of treatment of congenital clubfoot was introduced by Denis Browne in 1933, in which the feet were strapped to metal plates connected by a cross bar. Correction was obtained by forceful kicking on the part of the infant. This procedure was reintroduced and modified by Thomson of Toronto in 1942 and has greatly facilitated the early correction of congenital clubfeet.⁸⁷ It has proved a valuable adjunct to the usual methods of correction by manipulation and plaster casts. Emphasis should be placed on the institution of early treatment, since this technic is particularly applicable to the newborn infant, and the earlier treatment is instituted, the better the end-result.

theories are listed in a recent review.¹¹⁷ One report presents questionable evidence and analysis implicating heredity as the basis of the disorder.¹¹⁸ The wide variations of clinical appearances of this disorder are now apparent. These range from the association with meconium ileus in the newborn to the chance finding of patients five to nine years of age in relatively sound states of nutrition and with minimal pulmonary signs.

In the original reports most of the infants died before two years of age. The present therapeutic efforts appear to be increasing the survival period of these patients. Such treatment comprises provision of an adequate diet, substitution therapy in the form of pancreatin and attack on the pulmonary lesions so far as superimposed infection is concerned. In this connection Farber¹¹⁹ has emphasized the presence of a basic lesion in the lungs dependent on the production of abnormal secretions by the mucous glands. Some exception has been taken to this view in a recent report by Wigglesworth,¹¹⁷ but this point is of paramount importance in a consideration of therapy for pulmonary lesions. If altered secretions form the basis of the disease in the lungs, little can be expected from the effort aimed at eradication of superimposed infection. On the other hand, if the infection that is frequently present constitutes a significant portion of the pathologic process in the lungs, it is imperative to focus therapeutic effort toward its eradication, and the results to be expected might be more favorable. The use of sulfonamides orally and of penicillin intramuscularly has met with only partial success in the control of infection. Recently, the use of penicillin and sulfonamides in the form of aerosol inhalation therapy has provided a new approach to the treatment of intrapulmonary infections.^{120, 121} Experience reported recently indicates that the pulmonary lesion can be considerably influenced by this sort of treatment.¹²² A number of patients have shown considerable clearing of the pulmonary infiltration, with corresponding improvement in their clinical well-being, as revealed by a gain in weight and subsidence of cough and fever. It is quite clear, however, that the entire pulmonary lesion is not obliterated, since much of the infiltration remains and some wheezing or cough may persist. Furthermore, the patients are still extremely susceptible to recurrences of pulmonary infection.

Complete descriptions of the roentgenologic features of this disease have appeared.¹²³ In Neuhäuser's¹²⁴ paper particular attention has been devoted to the roentgenologic characteristics of meconium ileus, with the elucidation of certain helpful diagnostic signs.

There is a genuine need for a simpler means of establishing the diagnosis of fibrosis of the pancreas once it is suspected. A new approach to this problem utilizes a rise in amino acid level in the blood following a test meal.¹²⁵ In patients with fibrosis of the

pancreas who have no enzymes in the duodenum, there is little fluctuation of the postprandial amino acid level. Other chronic disturbances of intestinal absorption, such as celiac disease, in which there are normal enzymes in the duodenum, show a significant and comparatively high rise of amino acid level in the blood after the test meal.

Celiac Disease

The reports of the successful treatment of adult sprue with folic acid naturally arouse curiosity concerning similar effects in celiac disease of childhood.¹²⁶ In this clinic we have treated 8 well established cases of this disorder with folic acid without any effects on the steatorrhea or any of the other clinical or laboratory features of the disease.¹²⁷ Two patients with the diagnosis of celiac disease were treated by English physicians with folic acid, and benefit was reported.^{128, 129}

REFERENCES

- 63 Davis C M. Self selection of diet by newly weaned infants: experimental study. *Am J Dis Child* 36:651-679 1928
- 66 Levy D M. Experiments on sucking reflex and social behavior of dogs. *Am J Orthopsychiat* 4:203-224 1934
- 67 Sprock B. Avoiding behavior problems. *J Pediatr* 27:361-362 1945
- 68 Aldrich C. *Co-ordinating the Child's Appetite*. 137 pp. New York: MacMillan Co. 1934
- 69 Gesell A, Ilg F L, Learned J, and Ames L B. *Infant and Child in the Culture of Today: The guidance of development in home and nursery school*. 299 pp. New York: Harper & Bros. 1943
- 70 Livingston S and Kajdi L. Importance of heredity in prognosis of febrile convulsions. *Am J Dis Child* 69:524 1945
- 71 Bridge E M and Livingston S. Unpublished data
- 72 Crump E P. Convulsions in infants and children: age and etiologic incidence. *Lancet* 65:182-184 1945
- 73 Yarnett H. Diagnostic classification of patients with mental deficiency: distribution of 1,550 institutionalized patients with review of incidence of convulsive disorders and noncerebral developmental anomalies. *Am J Dis Child* 70:88-89 1945
- 74 Buchanan D. Convulsions in infancy and childhood. *N Clin North America* 30:163-172 1946
- 75 Lennox W G. Petit mal epilepsies: their treatment with tridione. *J A M A* 129:1069-1074 1945
- 76 *Idem*. Tridione in treatment of epilepsy. *J A M A* (in press)
- 77 Thorne F C. Anticonvulsant action of tridione: preliminary report. *Psychiatric Quart* 19:686-691 1945
- 78 Perlstein M A and Andelman M B. Tridione: its use in convulsive and related disorders. *J Pediatr* 29:20-40 1946
- 79 Harrison F F, Johnson R D and Ayer D. Fatal aplastic anemia following use of tridione and hydantoin. *J A M A* 132:11 1946
- 80 MacKav R P and Gottstein W K. Aplastic anemia and agranulocytosis following tridione. *J A M A* 132:15-16, 1946
- 81 Jepson P N. Use of prostigmine in management of infantile cerebral paralysis. *J Pediatr* 28:65-68 1946
- 82 Kabat H and Knapp M E. Mechanism of muscle spasm in poliomyelitis. *J Pediatr* 24:123-17 1944
- 83 Crothers B. Mechanism of labor from neurologic point of view. *J A M A* 92:99 1929
- 84 Biers R K. Tonic neck reflexes in children considered from prognostic standpoint. *Am J Dis Child* 55:696-742 1938
- 85 Lord E E. *Children Handicapped by Cerebral Palsy: Psychological factors in management*. 105 pp. New York: Commonwealth Fund 1937
- 86 Crothers B, Lord E and McGinnis M. Prognosis after encephalopathy in infancy. *J Mt Sinai Hosp* 9:376-385 1942
- 87 Bell J F and Grace D S. Treatment of congenital talipes equinovarus with modified Denis Browne splint. *J Bone & Joint Surg* 26:199-211 1944
- 88 Lichtenstein L and Jaffe H L. Eosinophilic granuloma of bone with report of case. *Am J Path* 16:595-604 1940
- 89 Green W T and Farber S. Eosinophilic or solitary granuloma of bone. *J Bone & Joint Surg* 24:499-526 1942
- 90 Green W T. Shipping of upper femoral epiphysis: diagnostic and therapeutic considerations. *Arch Surg* 50:19-33 1945
- 91 Klein A, Joplin R J and Reidy J A. Treatment in cases of slipped capital femoral epiphysis at Massachusetts General Hospital. *Arch Surg* 46:681-686 1943
- 92 Special Article. Evaluation of results of treatment in infantile paralysis. *J A M A* 4:128-21 1945

In all methods of equalizing leg length, careful and accurate measurements at various intervals are essential. A useful procedure of accurately measuring the bones of the lower extremities has recently been introduced.⁹⁹ It is essential that physicians in pediatrics and general practice appreciate the possibility of equalizing leg lengths and thus of preventing serious deformities in adult life. Children with lower extremities of unequal length should be referred for orthopedic treatment long enough before the time of natural closure of the epiphyses so that equalization by arrest is possible.

GASTROINTESTINAL DISORDERS

Acute Diarrheal Disease

Progress in the understanding of the causes of diarrheal disease has received considerable impetus from recent work on the isolation of viruses from patients with diarrhea.¹⁰⁰⁻¹⁰³ These studies are particularly stimulating because the search for a causative organism in the form of bacteria has frequently been disappointing. In spite of the tremendous reduction in the incidence of diarrhea there has continued to be frequent epidemic and endemic diarrhea whose cause remains obscure.

The use of the gamma-globulin fraction of human serum had no influence on the course or mortality of infants suffering from epidemic diarrhea of the newborn.¹⁰⁴ It will be of interest to watch the result of further studies along these lines, provided that viruses are found as a frequent cause of diarrhea.

Great progress has been made in the past decade in the treatment of the effects of diarrhea by repair solutions calculated to correct dehydration and acidosis. The importance of establishing renal function as an initial phase in the correction of the disturbed serum electrolyte pattern has been re-emphasized in a recent report.¹⁰⁵ It is opportune that this should be stressed in the light of current developments in elaboration of repair solutions. It should never be forgotten that the most sophisticated repair solution cannot be depended on to replace the wisdom of an alert and capable kidney in restoration of the normal electrolyte pattern.

Up to the present attention has been focused mainly on the major deficits of sodium and chloride resulting from diarrhea. It has long been recognized that other deficits existed, not only in the blood plasma but also in the intracellular electrolyte system.^{106, 107} Particular interest now centers on the deficit of potassium. Further information regarding the loss of potassium from the body during diarrhea is provided by recent contributions.¹⁰⁸ That potassium may be provided in a satisfactory solution and this deficit safely corrected has also been reported.^{109, 110} Details for the preparation and use of this repair solution are given in these reports. In the group of patients receiving this treat-

ment, the mortality was considerably reduced, and some of the symptoms were apparently relieved.

It is difficult to determine the symptoms that can be attributed to a deficit of potassium. Symptoms expected from low levels of serum potassium are those secondary to impaired functioning of striated muscle—for example, diaphragmatic and myocardial paralysis.¹¹¹ Considerable definition of all symptoms is still required. Furthermore, mortality alone may not suffice for the complete evaluation of any beneficial effects of the addition of potassium to a repair solution. This has been illustrated by the recent experience of attempting to evaluate the usefulness of amino acid-containing solutions to replace the nitrogen deficit that occurs in acute diarrhea. The validity of repair solutions to provide materials that correct all deficits occurring in acute diarrhea will be most adequately appraised when the results in patients suffering from all types of diarrhea can be evaluated, in contrast to the results in a single epidemic of diarrhea.

A note of warning is pertinent regarding certain dangers involved in the parenteral administration of solutions containing potassium ion. In patients suffering from dehydration and acidosis, the level of potassium in the serum may already be somewhat elevated.¹¹⁰ If further potassium is supplied by a repair solution either before renal regulatory mechanisms are restored or too rapidly, the level of potassium in the serum may reach a toxic level—an accident that actually occurred in an infant under such therapy.¹¹² This serves to re-emphasize the basic consideration that the restoration of renal function with sodium chloride and glucose solutions should be the initial phase of therapy.

Patients in a severe state of disturbed serum electrolyte pattern associated with either adrenocortical insufficiency or renal failure might well have their fate imperiled by potassium-containing solutions if the condition were not suspected. Such patients are regularly encountered.^{113, 114} In this clinic we have already had a nearly disastrous result from the administration of a potassium-containing repair solution to a child presumably suffering from adrenocortical insufficiency even though urine flow had been first re-established with glucose and sodium chloride solutions.

It now appears that sulfadiazine is as useful as any of the more specialized sulfonamides, such as succinylsulfathiazole and sulfaguanidine, in the treatment of the acute bacterial dysenteries in infants and children.¹¹⁵

Oral streptomycin has been advocated and used with some success in the treatment of infectious diarrhea due to specific sensitive enteric organisms.¹¹⁶

Fibrosis of the Pancreas

Clinical and pathological reports concerning this disease continue to appear with regularity. The cause of the disorder remains obscure. The current

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

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CASE 33241

PRESENTATION OF CASE

A sixty-three-year-old man was admitted to the hospital because of heartburn and abdominal pain.

He complained of heartburn for the previous two years with a dull, constant occasionally sharp pain across the upper abdomen that had extended into the back, especially in the right infrascapular region, in the preceding two months. "Pills" had no effect on the pain, but he felt better when lying on the left side. Three months prior to admission a gastrointestinal series at an outside hospital showed no evidence of ulcer but did show a diaphragmatic hernia. Immediately following the x-ray studies the patient ate a heavy meal, with subsequent repeated vomiting for one day. About that time he noticed slight constipation and subsequently had two black stools. About a month and a half before admission painful ankle edema and occasional shoulder, elbow and wrist pains began. He also noted increasing weakness and a weight loss of 25 pounds in the three months prior to admission.

Physical examination revealed a well developed man showing evidence of recent weight loss. A Grade I apical systolic murmur was noted, with occasional extrasystoles but no enlargement of the heart. The lungs were clear. There was slight tenderness to palpation just beneath the right costal margin, but the liver and spleen were not felt. A few observers felt a deep but indefinite palpable mass in the right upper quadrant. There was a ++ to +++ pitting edema of the lower legs, more so on the right. The temperature was 100°F, the pulse 96, and the respirations 20. The blood pressure was 130 systolic, 80 diastolic.

Examination of the blood showed a hemoglobin of 13 gm and a white-cell count of 16,500, with 71 per cent neutrophils. The urine was normal, as were the stools. The serum protein was 6.2 gm per 100 cc, with an albumin-globulin ratio of 0.9. The nonprotein nitrogen, prothrombin time, amylase and fasting blood sugar were within normal limits. A blood Hinton test was negative. A Graham test did not reveal a gall-bladder shadow.

An intravenous pyelogram was essentially normal. There were old compression deformities of the fourth and fifth lumbar vertebrae and moderate degenerative changes of the spine. An x-ray film of the chest revealed moderate scoliosis of the thoracic spine, with a convexity to the right, and calcification of the wall of the aortic arch. A barium enema disclosed no evidence of intrinsic disease. The gastrointestinal series revealed a small hiatus hernia that reduced itself while the patient was in the upright position. No other abnormality was found.

On the fourth hospital day following an enema the patient began to perspire and fainted. He stated that he had passed a large black stool, but he was on iron therapy and the feces were not saved for examination. During the night of the fourth hospital day he had a severe attack of epigastric pain, which was relieved by firm rubbing of the upper abdomen. The following afternoon, ten minutes after finishing lunch, he developed a boring pain running from front to back in the epigastrium without nausea or vomiting. Sitting up did not relieve the pain. Another Graham test showed no filling of the gall bladder. Duodenal drainage on the seventh hospital day revealed clear, yellow fluid but no sign of blood. Examination of the material disclosed numerous bile-stained white cells and crystals. A cephalin-flocculation test was + + +, both in twenty-four and in forty-eight hours. The serum amylase determination was 29 units, the blood calcium 7.2 mg and the phosphorus 3.7 mg per 100 cc, and the phosphatase was 4.5 units. An electrocardiogram was normal. In a bromsulfalein test the five-minute sample was too dark to read, and in forty-five minutes there was 22 per cent retention of the dye. Subsequent to the duodenal drainage the patient developed a fever, the temperature rising to 101°F. each day, and the pain was rather severer than at the time of entry.

At the end of two weeks the temperature became normal, and on the seventeenth hospital day a laparotomy was performed. At operation no abnormalities could be discovered on palpation or inspection of the abdominal viscera. Because of the positive Graham test on two occasions and the pus and crystals in the duodenal drainage, the gall bladder was removed from above downward without incident. The common duct, which was then opened and explored, contained clear bile, and probes passed readily into the duodenum. A liver biopsy was also performed.

On the fourth postoperative day the patient complained of upper abdominal pain similar to that before operation. The next day he complained of numbness and paresthesias in the hands, and neurologic examination revealed diminished sensation to pinprick in the distal phalanges of the left hand and over the lateral aspect of the right lower leg and foot. On the following morning the patient awoke complaining bitterly of pain and inability to

- 93 Green, W T Diagnostic and therapeutic consideration in anterior poliomyelitis *Rhode Island M J* 28 89 93, 1945
- 94 Kenny, E *The Treatment of Infantile Paralysis in Acute Stage* 285 pp Milwaukee Bruce Publishing Co, 1941
- 95 Altemeier, W A and Helmsworth J A Penicillin therapy in acute osteomyelitis *Surg, Gynec & Obst* 81 138 157, 1945
- 96 Key, J A Penicillin and sulfonamides in treatment of osteomyelitis and pyogenic arthritis *Bull New York Acad Med* 21 87-98, 1945
- 97 Anderson, D G Howard L G, and Rammelkamp C H Penicillin in treatment of chronic osteomyelitis report of 40 cases *Arch Surg* 49 245 257, 1944
- 98 Reidy J A Barr, J S, and Lingley, J R Unpublished data
- 99 Green W T Wyatt G M, and Anderson, M Orthoroentgenography as method of measuring bones of lower extremities *J Bone & Joint Surg* 28 60-65 1946
- 100 Lyon, G M and Folsom T G Epidemic diarrhea of newborn I Clinicoepidemic, pathologic and therapeutic aspects *Am J Dis Child* 61 427-444 1941
- 101 Light J S, and Hodes, H L Studies on epidemic diarrhea of new born isolation of filtrable agent causing diarrhea in calves *Am J Pub Health* 33 1451-1454 1943
- 102 Buddingh, G J and Dodd K Stomatitis and diarrhea of infants caused by hitherto unrecognized virus *J Pediat* 24 105 113 1944
- 103 Buddingh G J Virus stomatitis and virus diarrhea of infants and young children *South M J* 39 382 390 1946
- 104 High, R H Anderson, N A and Nelson, W E Further observations of epidemic diarrhea of newborn observation of biphasic type of clinical course therapeutic measures including prophylactic and therapeutic use of gamma globulin *J Pediat* 28 407-417, 1946
- 105 Levine, S Z Parenteral repair of dehydration *J Pediat* 26 196-201 1945
- 106 Holt L E Courtney, A M, and Fales, H L Chemical composition of diarrheal as compared with normal stools in infants *Am J Dis Child* 9 213 224 1915
- 107 Butler A M McKhann C F and Gamble J L Intracellular fluid loss in diarrheal disease *J Pediat* 3 84-92, 1933
- 108 Darrow D C Body fluid physiology relation of tissue composition to problems of water and electrolyte balance *New Eng J Med* 233 91 97 1945
- 109 *Idem* Retention of electrolyte during recovery from severe dehydration due to diarrhea *J Pediat* 28 515 540 1946
- 110 Govan C D Jr and Darrow D C Use of potassium chloride in treatment of dehydration of diarrhea in infants *J Pediat* 28 541-549 1946
- 111 Holler J W Potassium deficiency occurring during treatment of diabetic acidosis *J A M A* 131 1186-1189, 1946
- 112 Govan, C D Jr and Weiseth W M Potassium intoxication report of infant surviving serum potassium level of 12.27 millimoles per liter *J Pediat* 28 550-553, 1946
- 113 Wilkins L Fleischmann, W, and Howard J E Macrogonitosmia praecox associated with hyperplasia of androgenic tissue of adrenal and death from corticoadrenal insufficiency case report. *Endocrinology* 26 385-395 1940
- 114 Thelander H E Congenital adrenal cortical insufficiency associated with macrogonitosmia follow up and terminal report. *J Pediat* 29 213 221 1946
- 115 Menchaca F J Sulfadiazine in treatment of diarrhea in children. *Am J Dis Child* 68 5, 1944
- 116 Nichols, D R, and Herrell, W E Streptomycin its clinical uses and limitations *J A M A* 132 200-206, 1946
- 117 Wigglesworth, F W Pathology and bacteriology fibrocystic disease of pancreas *Am J M Sc* 212 351 365 1946
- 118 Andersen, D H, and Hodges R G Celiac syndrome V Genetics of cystic fibrosis of pancreas with consideration of etiology *Am J Dis Child* 72 62 80 1946
- 119 Farber, S Pancreatic insufficiency and celiac syndrome *New Eng J Med* 229 653-657 and 682 687 1943
- 120 Barach A L Inhalation treatment of bronchial asthma *New York State J Med* 46 1002-1008 1946
- 121 Barach A L, Garthwaite B and Rule C Use of penicillin aerosol in bronchopulmonary and sinus infections *New York State J Med* 46 1703-1713, 1946
- 122 di Sant'Agnese P E A, and Andersen D H Celiac syndrome IV Chemotherapy in infections of respiratory tract associated with cystic fibrosis of pancreas observations with penicillin and drugs of sulfonamide group with special reference to penicillin aerosol *Am J Dis Child* 72 17-61 1946
- 123 Pugh D G Fibrocystic disease of pancreas. *Am J M Sc* 210 681 687, 1945
- 124 Neuhauser, E B D Roentgen changes associated with pancreatic insufficiency in early life *Radiology* 46 319 328 1946
- 125 West, C D, Wilson, J L, and Eyles R Blood amino nitrogen levels changes in blood amino nitrogen levels following ingestion of proteins and of protein hydrolysate in infants with normal and with deficient pancreatic function *Am J Dis Child* 72 251 273 1946
- 126 Darby, W J Jones E and Johnson, H C Use of synthetic L casei factor in treatment of sprue *Science* 103 108, 1946
- 127 May C D, and Utz, D W Personal communication
- 128 Brody, H P, and Gore, L Folic acid in celiac disease *Lancet* 2 618, 1946
- 129 Dalton H W, Thomson M I and Wilson, V K Folic acid in celiac disease *Lancet* 2 652, 1946

perhaps spoil the fun of these exercises — that is, fun for you but not for me. I thought that, instead of going round and round this diagnostic circle, I should take one symptom and see what I could do with it.

The peculiar complication of this case is the peripheral neuritis. I do not believe that it was due to nutritional deficiency, I say so because of the onset. The pain, which was sudden in its development, was patchy and not symmetrical, and hardly compatible with a diagnosis of nutritional deficiency.

Was the prothrombin time normal?

DR JONES: Yes.

DR RICHARDSON: What about infectious polyneuritis? I have never seen a patient with this disease who reacted in this fashion. Many of the

metastases and no evidence of tumor on abdominal exploration.

A final possibility is some other type of central-nervous-system infection or neoplastic invasion. There is no report of a lumbar puncture. Nothing in the blood picture supports a diagnosis of sepsis, although the patient was running a mild fever.

Could this neuritis have been arterial in origin? I do not understand why, when an artery becomes plugged, neuritic symptoms appear. I do not want to go more deeply into this question.

Periarteritis nodosa is a diffuse disease associated with neuritis, fever and abdominal pain, and that diagnosis must be considered in this case. Again, the onset of the neuritis was peculiar for periarteritis nodosa. The type of abdominal pain due



FIGURE 1

facial nerves are first involved, and sometimes these are the only nerves affected. There are other types of infectious polyneuritis, but I do not believe that there is much evidence for obscure diseases.

Did this man have active tabes, with everyone thrown off the track? The pain of tabes is not of this type. Usually, it involves the lower limbs, with, in the early stages, no definite evidence of impaired sensation.

What about metastases to bone or malignant tumor in the region of the sacral or brachial plexuses? This has not been ruled out and remains a possibility, although there was no x-ray evidence of bone

to small mesenteric thrombosis or infarctions is usually referred to the midline and is more generalized. Although one should bear in mind the possibility of periarteritis nodosa, I do not believe that in this case one can make such a clear-cut diagnosis. I come down to the fantastic theory that this man had arterial disease, which was perhaps localized in the region of the abdominal aorta, at the level of the pancreas. All this midepigastrie boring pain going through to the back is quite typical of pancreatic pain, or pain in that area. I suspect that the patient had an ulcerating lesion in the region of the pancreas, with erosion into the aorta and actual

move the left foot. Physical examination showed no change in color or temperature of the foot. There was anesthesia over the entire leg below the knee except for a 5-cm. band along the medial aspect.

DIFFERENTIAL DIAGNOSIS

DR. WYMAN RICHARDSON: I might begin by saying that I have arrived at a fantastic conclusion, and that I apologize ahead of time for it.

"A few observers felt a deep but indefinite palpable mass in the right upper quadrant." I think that one must forget about this mass, with only a few observers feeling a deep but indefinite mass; it remains deeply obscure and quite indefinite to me.

This is a case in which a blood smear would have been helpful in the differential diagnosis. I shall point out here that a leukocytosis of this extent, with only 70 per cent neutrophils, is strong evidence against pyogenic infection as the cause of the symptoms, and also against bacterial endocarditis alone as the cause of the symptoms. The blood picture suggests fairly recent and acute blood loss or infarction, or if there were evidence of red-cell regeneration it would suggest the possibility of bone-marrow encroachment. We do not know whether there was red-cell regeneration or not. There are other kinds of infection that might cause this type of blood picture, but without further data, I do not believe that one need consider them. This picture is compatible with loss of blood into a cavity or with extravasated blood.

I assume that a good many stool examinations for occult blood were done and were negative.

I wonder why the albumin and globulin were not reported in grams, rather than the albumin-globulin ratio. It is easier for me if the report is in grams, my mathematics not being too good. In this case I should say that there was about as much albumin as globulin.

Perhaps we should see the x-ray films. I am anxious to know if there is any evidence suggesting tumor involving bone in either the lumbar or the cervical spine. I do not believe that films of the cervical spine were taken, however.

DR. TOUFIC KALIL: The only thing that I can see is the hiatus hernia that was described as being readily reducible on standing.

DR. RICHARDSON: I am uncertain whether the hiatus hernia accounted for this man's pain. Do you see the deep and indefinite mass in the right upper quadrant? Nothing was observed in that area at operation.

DR. KALIL: No.

DR. RICHARDSON: Is this an old fracture of the spine?

DR. KALIL: All the bones are decalcified. Without a lateral view of the lumbar spine, one cannot tell much about it. There is no localized destruction. The intravenous pyelogram is normal.

DR. RICHARDSON: The question is, Did this man faint because he had a sudden hemorrhage? I should say that a man who fainted suddenly from hemorrhage would not immediately pass a black stool. To account for the fainting, he would have to have had a massive hemorrhage, and if he immediately passed a stool it would definitely have been bloody. What else could happen to a man who had an enema? I suppose that many things could occur. Patients may feel faint without any pathologic reason. I think that this episode may have been significant, although I am not quite sure of what. One could have perforation of the bowel following an enema, but there was no evidence of peritonitis following it. For the moment I shall say that perhaps something occurred when the enema was given. It may turn out to be of some importance, but it was probably not a sudden acute hemorrhage. No guaiac-positive stools were reported following this incident.

The record does not state whether the crystals found in the duodenal drainage were cholesterol or bilirubin. I do not rely too much on the cephalin-flocculation test. I wonder if it was associated with the slight increase in globulin. The serum amylase was 29 units per 100 cc. I believe that is normal. Do you agree, Dr. Jones?

DR. CHESTER M. JONES: Yes.

DR. RICHARDSON: The blood calcium was somewhat low, as was the serum albumin. I do not know whether that is significant or not. The bones were somewhat decalcified. Most of the blood chemical findings were normal. The phosphorus was slightly high but, I should think, within normal limits.

It is not stated whether the bromsulfalein test was done with a 2-mg. or a 5-mg. dose, presumably, it was 5 mg. I should say that there was slight increase in bromsulfalein retention but within a range that was not sufficiently characteristic to lead to any specific diagnosis. At least, I shall say that it was not severe enough to make it certain that there was any considerable degree of hepatic failure.

Evidently, it was considered quite possible that this man had gallstones. I cannot imagine that the surgeon did not open the gall bladder, and I gather that no stones were found, although nothing is said. I believe that the gall bladder was removed more or less on theoretical grounds.

The record does not mention peripheral arterial pulsation, which I think is extremely important in this case.

One of the things that helps a great deal in these discussions is the knowledge that the patient died. I do not know whether this patient died or whether he got well. I might say that I am doubtful if Dr. Castleman can make a diagnosis on the basis of a small liver biopsy, and I suspect that he had more material to examine than a small piece of liver. I assume that the patient's subsequent course was so characteristic as to give the diagnosis away and

DR RICHARDSON Regarding the nonfilling gall bladder, I meant to suggest that it might have been due to a poorly functioning liver. It will be recalled that there was some degree of dye retention.

CLINICAL DIAGNOSIS

Carcinoma of body of pancreas?

DR RICHARDSON'S DIAGNOSIS

Ulcerating lesion, pancreatic region, causing aortic erosion and dissection

ANATOMICAL DIAGNOSES

Periarteritis nodosa involving gall bladder and liver
Infarcts of gall bladder

PATHOLOGICAL DISCUSSION

DR CASTLEMAN The gall bladder that we received looked fairly normal except for a few small, dark, hemorrhagic, questionably ulcerated areas on the mucosa. The rest of the mucosa was smooth, shining and velvety. On microscopical examination we found in the wall of the gall bladder many arteries whose walls were necrotic and heavily infiltrated with polymorphonuclear leukocytes and lymphocytes. The findings were quite characteristic of periarteritis nodosa. Elastic-tissue preparations showed marked destruction of the elastica. Some of the vessels were thrombosed and accounted for the focal mucosal ulcerations, which were really focal infarctions (Fig 1). We found the same process on liver biopsy — extensive necrosis of the small arteries, with thrombosis. In places organization of the thrombi with recanalization had occurred (Fig 2).

This man is still on the ward, Dr Richardson, and we do not know what the final situation is. Can you tell us how he is, Dr Dahl?

DR LEWIS K DAHL He is going downhill rapidly.

DR RICHARDSON Did he ever have any eosinophilia?

DR DAHL No.

DR RICHARDSON Had he ever been given any sulfonamides?

DR DAHL We could not obtain any history of sulfonamide administration. The patient does not speak English very well, but he gave no history of taking tablets that suggested the sulfonamides.

DR RICHARDSON What was the anatomic cause of the boring epigastric pain?

DR CASTLEMAN I believe that the infarction of the gall bladder could have caused the pain.

CASE 33242

PRESENTATION OF CASE

A seven-month-old male infant was admitted to the hospital because of a mass in the right abdomen. The child was born after an uneventful pregnancy and weighed 8 pounds, 12 ounces. Development

was normal, and the day before admission his mother first noticed a mass in his right abdomen.

Physical examination showed an overnourished infant in no distress. There was a firm, rounded, fairly smooth, nontender mass occupying the right half of the abdominal cavity and extending from beneath the right costal margin to just below the level of the right iliac crest. The rest of the examination was negative.

Examination of the blood revealed a white-cell count of 19,600, with 49 per cent neutrophils, 45 per cent small lymphocytes, 4 per cent monocytes and 2 per cent eosinophils. Urine and stool examinations were negative. An intravenous pyelogram revealed an unusually large right kidney, which was smooth. The left was obscured by gas but appeared within normal limits. The right kidney produced bulging of the abdominal wall laterally. Excretion of dye was prompt in both kidneys. The urinary passages on the left were poorly seen but showed no gross abnormality. On the right there was gross crowding of the calyces in the upper half of the kidney upward and of the lowermost calyx downward and inward. There was no evidence of gross invasion of the calyces or pelvis.

On the fifth hospital day an exploratory laparotomy was performed.

DIFFERENTIAL DIAGNOSIS

DR LEO BURGIA This brief history leads one at once to the problem of the etiology and nature of an abdominal mass in a seven-month-old infant who had previously been well.

The x-ray report of an enlarged kidney producing bulging of the abdominal wall suggests that the mass was at least retroperitoneal. This simplifies matters somewhat in that a host of abdominal possibilities, such as congenital cysts, reduplications, hepatoma, abdominal lymphoma and Hodgkin's disease, may be excluded.

Since we have decided that the tumor mass was retroperitoneal, our next consideration is whether or not it was malignant and finally, what was its nature. From a practical standpoint one should follow Farber's* generalization, "Every solid mass in an infant or child should be regarded as a malignant tumor and removed in its entirety for histological examination and determination of its exact nature." Presumably, this was carried out in the present case.

For purposes of discussion we should rule out a "benign" condition such as cystic disease of the kidney — multiple or single. There is no evidence of abnormal kidney function such as albuminuria or hematuria. Of course, with small cysts there may be sufficient normal renal tissue for an infant of this age. With a mass such as that described, how-

*Farber, S. Malignant tumors in early life. In *Textbook of Pediatrics*, Fourth edition, 1320 pp. Philadelphia: W. B. Saunders Company, 1945. Pp. 315-323.

dissection of the aorta up and down. He may have had a moderate degree of cirrhosis of the liver, but I do not believe that it was significant. If this is not a fantastic diagnosis, I have never heard of one.

DR. WALTER BAUER: I believe that you should not have lost the diagnosis of periarteritis nodosa.

DR. RICHARDSON: I was going to flip a coin but then decided on a flat-footed diagnosis.

DR. BAUER: The white-cell count was 16,000, which is suggestive, and the other symptoms are readily explained on the basis of periarteritis nodosa. It certainly accounts for the recurring at-

DR. BENJAMIN CASTLEMAN: Will you tell us about the operation, Dr. Taylor?

DR. GRANTLEY W. TAYLOR: I should apologize for operating at all. The patient had lost a good deal of weight, had become progressively weak and had a somewhat elevated white-cell count and intermittent fever. The most incapacitating symptom was the severe pain that went through to the back. The only evidence that we could tie up with that as possibly being helpful was the character of the duodenal drainage and the two positive Graham tests. There was no jaundice, and we thought that

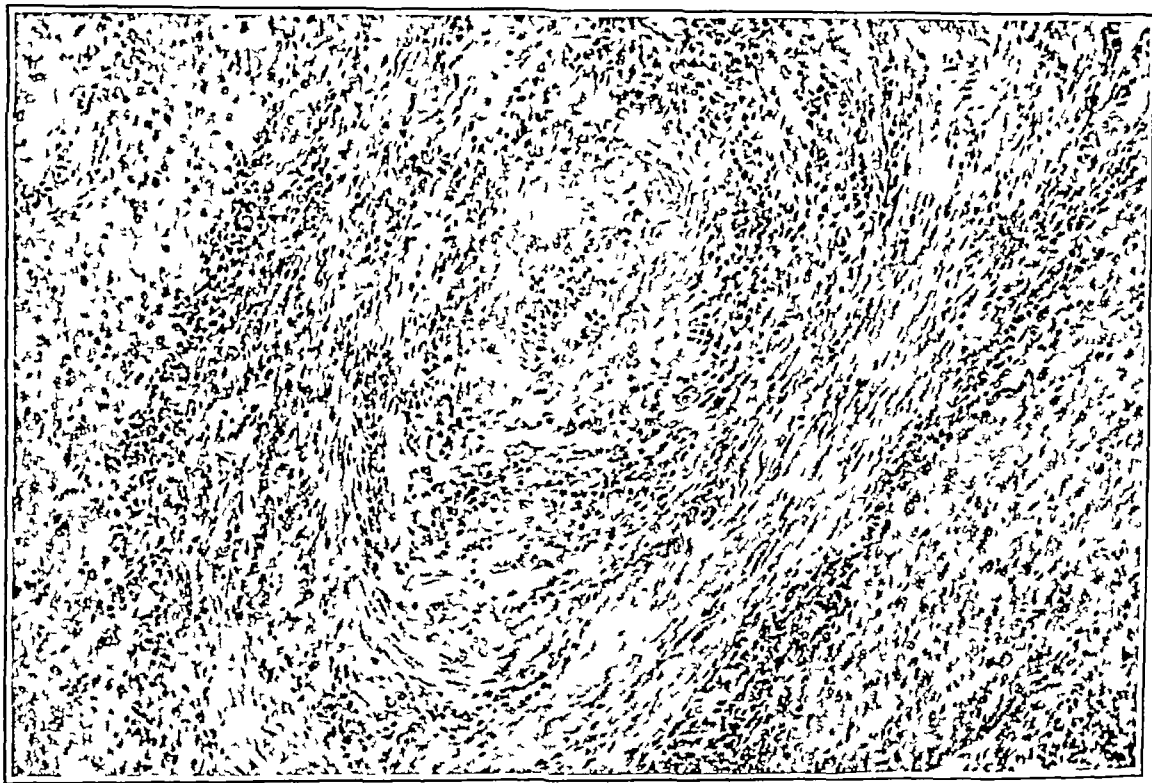


FIGURE 2

tacks of abdominal pain. I should make a diagnosis of periarteritis nodosa.

DR. RICHARDSON: I accept that as a possible diagnosis. I doubt if the patient had it. Does anyone else want to suggest an alternative diagnosis?

A PHYSICIAN: How about acute porphyria? Would it fit in with the findings in this case?

DR. RICHARDSON: I had not thought of porphyria as a disease. I considered lead colic and neuritis, which I did not think probable. I am not able to rule out acute porphyria.

DR. JONES: We had a case of porphyria six weeks ago with repeated attacks of severe abdominal pain, and I think that that condition should be included at least in the differential diagnosis.

all these symptoms might have occurred on the basis of carcinoma involving the body of the pancreas or that the patient had disease related to the gall bladder and common duct. I must say that it was a completely negative exploration. The hiatus hernia did not seem to account in any way for the symptomatology. Then the problem was what to do—whether to let him alone, sew him up or take out the gall bladder on the ground that the symptoms were due to gall-bladder disease that was not obvious from external examination of the organs. We also explored the common duct on the suspicion that cholangitis was present, but the bile duct proved to be perfectly normal. We removed the gall bladder and took a liver biopsy, thinking that we might turn up with something.

distorted pelvis but good function, and a normal urine in an otherwise normal infant suggests the presence of a mixed tumor of the right kidney. I believe that this infant had a Wilms's tumor.

DR STANLEY WYMAN: These films show the enlarged right kidney pressing on the lateral wall of the abdomen. The upper and lower calyces in this film are crowded upward and downward respectively, but no definite intrinsic involvement of the walls or the pelvis can be determined. No evidence of disease can be seen in the bones of the spine or chest.

CLINICAL DIAGNOSIS

Wilms's tumor of kidney

DR BURGIN'S DIAGNOSIS

Wilms's tumor of kidney

ANATOMICAL DIAGNOSIS

Wilms's tumor of kidney

PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN: At operation Dr Robert R. Linton found a large tumor of the kidney, which he removed without difficulty. It was not adherent to any of the surrounding structures and had not broken through the capsule of the kidney. The tumor measured about 8 cm in diameter and had replaced most of the renal parenchyma, leaving only a narrow rim of cortex (Fig. 1). It appeared to be completely surrounded by a fibrous capsule and did not invade the pelvis or calyces. Microscopically, the tumor was composed of both tubular and spindle-cell elements, which are the characteristic findings in a Wilms's tumor or what is often called "embryonal adenocarcinoma." A few regional lymph nodes removed with the kidney showed only hyperplasia.

ever, one would expect some abnormal urinary findings if it had been due to cystic disease. One would also expect more distortion of the renal pelvis, possibly with an x-ray appearance consistent with the so-called "spider pelvis" deformity. The latter picture is by no means diagnostic of this condition, which has been reported in cases of embryoma of the kidney. Cystic disease is generally bilateral—in 98 per cent of cases, according to some authors

retroperitoneal space and about the adrenal glands. There is no characteristic picture other than the presence of an abdominal mass. One may encounter nonspecific complaints of fever, anorexia, bowel disturbances and so forth. If there has been metastasis to bone, and this is common with neuroblastoma, there may be pain in the extremities.

Embryoma of the kidney is an encapsulated tumor arising within the kidney. The tumor is firm,

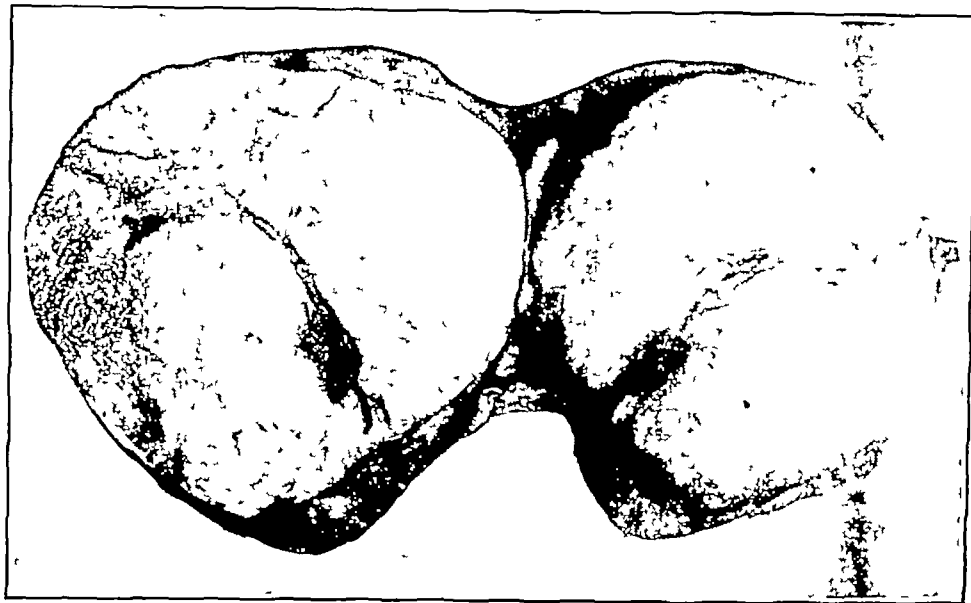


FIGURE 1

The prompt excretion of dye by both kidneys is further evidence against such a diagnosis.

With much of the previous evidence one can rule out hydronephrosis due to obstructive uropathy resulting from congenital malformations. Inflammatory processes may likewise be excluded. We might, in passing, mention such benign tumors as lipoma, fibroma and myoma only to note that these are extremely rare and not likely to produce the picture described here.

We are then led to consider at once some of the malignant tumors of this region. In children under two or three years of age the commonest tumors occurring in the renal region are the embryoma of the kidney (Wilms's tumor, or mixed tumor of the kidney) and tumors of the neuroblastoma series. One might also include occasional mixed tumors arising from tissues outside the kidney but in the retroperitoneal spaces. One should perhaps include hypernephroma. There seems to be some question whether such a tumor ever occurs in infancy. I do not believe that we need consider it in this case.

The neuroblastoma may arise within the adrenal medulla or from sympathetic nerve tissue in the

smooth and rounded in outline. It often extends to the midline and to the iliac crest. Since such tumors arise within the kidney, we expect to find distortion of the renal pelvis by x-ray examination. Occasionally, the deformity may be confused with that produced by cystic disease, as I have indicated above. The tumor is usually unilateral. Neuroblastoma occasionally arises within the kidney from inclusions of adrenal medullary tissue present there and consequently gives a picture indistinguishable grossly from embryoma.

The sudden appearance of the tumor one day before admission may be difficult to reconcile with the physical examination on admission. The life history of these tumors, however, includes such phenomena, generally, massive hemorrhage into a tumor that is starting to grow rapidly may make the tumor noticeable in cases in which examination a few days previously has revealed no mass. The elevated white-cell count may have been in response to the hemorrhage or necrosis, or both, that may have been taking place.

The sudden appearance of a firm, smooth tumor mass involving the kidney, with x-ray evidence of a

THE EFFECT OF DI-ISOPROPYL FLUOROPHOSPHATE ON PATIENTS WITH MYASTHENIA GRAVIS

MUSCULAR fatigue characteristic of the weakness in patients with myasthenia gravis is thought to result from an insufficiency of acetylcholine at the myoneural junction. This insufficiency may be due to a decreased formation of acetylcholine (faulty metabolism), to an increased cholinesterase activity destroying the acetylcholine more rapidly than under normal conditions or to a decreased activity of acetylcholine itself, possibly caused by the presence of an antagonistic curare-like substance. There is no unequivocal evidence at present to support a view that any one of these postulates accounts for the chief symptom of myasthenia gravis, but it is agreed by all investigators that the acetylcholine-cholinesterase balance is disturbed at the myoneural junction in this disease. It has been shown, moreover, that cholinesterase is inhibited by neostigmine or physostigmine, the two drugs ordinarily used in the treatment of this disease. Because of the ease with which it is tolerated by patients, neostigmine has replaced physostigmine.

Although neostigmine is reasonably efficient other cholinesterase agents are now under investigation. Recently, di-isopropyl fluorophosphate (DFP), a compound unrelated chemically to neostigmine, was found to produce inhibition of serum, red-cell, muscle and brain cholinesterase in animals. The results of treating myasthenic patients with this drug have now been reported by Comroe and his associates,¹ working at the University of Pennsylvania Medical School and the Medical Research Laboratory, Chemical Warfare Service, Edgewood Arsenal. Bodansky,² while working with the Chemical Warfare Service, first noted the inhibiting power of di-isopropyl fluorophosphate on cholinesterase. When given intramuscularly, it is capable of lowering plasma and red-cell cholinesterase activity to a marked extent and for a prolonged period. The drug is also capable of improving muscle strength in patients with myasthenia gravis. It is not, however, a satisfactory drug to use from the clinical point of view. In the 7 patients treated by Comroe et al., 2 showed little or no benefit, 2 were consider-

ably improved, 1 had marked beneficial effects, and in 2 the results were obscured by peculiarities in the natural cycle of the disease. In no case did the objective or subjective improvement following the administration of di-isopropyl fluorophosphate equal or exceed that produced by the use of neostigmine. Attempts, moreover, to give large doses of the drug resulted in nausea and vomiting and other symptoms referable to the central nervous system. Despite the fact that it lowered the plasma cholinesterase to zero, it produced less clinical improvement than neostigmine in patients with myasthenia gravis.

The reason for the relative failure of di-isopropyl fluorophosphate as a therapeutic agent has not been fully determined. Being a highly lipid-soluble agent whereas neostigmine is a highly water-soluble agent, it may not find its way into the myoneural junction as readily as does neostigmine. If the drug is given to man in doses large enough to produce improvement throughout the body, it cannot be administered regularly because of its untoward effects on the gastrointestinal tract and the nervous system. The better results obtained by neostigmine however may be due to the possibility that neostigmine has a direct action on skeletal muscles that is not shared by di-isopropyl fluorophosphate. Whatever final conclusions are reached regarding the reason for its relative failure, the drug may prove to be of some use when utilized, in nontoxic doses, to obtain its prolonged effect. At the same time neostigmine can be given to obtain the characteristically stronger action. Since neostigmine, however, tends to protect cholinesterase from inactivation by di-isopropyl fluorophosphate, it seems unlikely that the latter will ever be as valuable as neostigmine in the treatment of myasthenia gravis.

REFERENCES

1. Comroe J. H. Jr, Todd J, Gammon G. D, Leopold I. H, Koelle G. B, Bodansky O, and Gilman A. Effect of di-isopropyl fluorophosphate (DFP) upon patients with myasthenia gravis. *Am J Med Sci* 212:641-651 1946.
2. Bodansky O. Contributions of medical research in chemical warfare to medicine. *Science* 102:517-521 1945.

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DEATH

SNOW — Henry C. B. Snow, M.D., of Buzzards Bay, died May 27. He was in his seventy-first year. Dr. Snow received his degree from Tufts College Medical School in 1897. He was a former member of the Massachusetts Medical Society.

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MATERIAL should be received not later than noon on Thursday, three weeks before date of publication

THE JOURNAL does not hold itself responsible for statements made by any contributor

COMMUNICATIONS should be addressed to the *New England Journal of Medicine* 8 Fenway Boston 15, Massachusetts

BLUE SHIELD ADVANCES

ON JUNE 1, 1947, Blue Shield took an important step forward. On that date its present program of surgical and obstetric benefits in the hospital was extended to include medical (nonsurgical) benefits in the hospital and surgical and obstetric benefits outside the hospital. At the same time, a new schedule of fees for services rendered to holders of Blue Shield policies became effective.

Undoubtedly the latter will receive the utmost attention and a certain amount of criticism, particularly from those participating physicians who

are surgeons. The schedule is the result of careful study and of many time-consuming meetings of the committees appointed to prepare it. The committees were composed of specialists in their various fields, who agreed that Blue Shield fees should not be based on the customary value of a specialist's services but on the ability of individuals and families in the under-income group to pay for such services. Much consideration was given to the relative difficulty of procedures not only within the specialties but also between the specialties, with the result that procedures of comparable difficulty in, for example, ophthalmology and urology were assigned similar fees so far as it was possible to do so. At first glance the level of fees may seem low, but when it is remembered that they apply to low-income patients, many of whom were previously medically indigent and to patients who were formerly poor credit risks, their adequacy is more easily visualized. It should also be recognized that the schedule applies on a state-wide basis.

With nearly 600,000 persons covered, Blue Shield is now the second largest and one of the most prosperous medical-care plans in the Nation, and much of its success is attributable to the fact that physician participation, originally in the neighborhood of 50 per cent, has rapidly climbed to its present level of over 90 per cent. The Blue Shield Board of Directors, made up of one third physicians and two thirds lay persons, is elected by the Executive Committee of the Council of the Massachusetts Medical Society, and before any rules or regulations affecting medical matters can be implemented they must be approved by the Executive Committee. Furthermore, in each district medical society there is a Blue Shield Professional Service Committee, through which the practicing physician can make his voice heard.

The ultimate success of Blue Shield rests primarily on the degree to which the medical profession, collectively and individually, participates. Because of the overwhelming importance of this venture, every physician who is interested in maintaining the voluntary approach to the problem of the costs of medical care and who is not yet a participant should request that he be supplied with an application form. Such letters should be addressed to Massachusetts Medical Service, 38 Chauncy Street, Boston 11.

Carbohydrate Metabolism: Correlation of physiological, biochemical and clinical aspects By Samuel Soskin, M.D., director of the Research Institute, Michael Reese Hospital, medical director, Michael Reese Hospital, and professional lecturer in physiology, University of Chicago, and Rachmiel Levine, M.D., director of metabolic and endocrine research, Michael Reese Hospital 8°, cloth, 315 pp, with 42 tables Chicago University of Chicago Press, 1946 \$6.00

The Traumatic Deformities and Disabilities of the Upper Extremity By Arthur Steindler, M.D., professor and head, Department of Orthopedic Surgery, State University of Iowa College of Medicine. In collaboration with John L. Muner, M.D., associate, Orthopedic Department, State University of Iowa College of Medicine 4°, cloth, 494 pp, with 443 illustrations Springfield, Illinois Charles C Thomas, 1946 \$10.00

Operative Gynecology By Richard W. Te Linde, M.D., professor of gynecology, Johns Hopkins University School of Medicine, and chief gynecologist, Johns Hopkins Hospital 8°, cloth, 751 pp, with 309 illustrations and 9 color plates Philadelphia J. B. Lippincott Company, 1946 \$18.00

Diseases of the Basal Ganglia and Subthalamic Nuclei By D. Denny-Brown, M.D., ChC, D.Ph., FRCP, professor of neurology, Harvard Medical School, and director of Neurological Unit, Boston City Hospital 8°, cloth, 74 pp, with one colored plate New York Oxford University Press, 1946 \$2.50 Reprinted from *Oxford Loose-Leaf Medicine*

The Diagnosis and Treatment of Bronchial Asthma By Leslie W. Gay, Ph.D., M.D., assistant professor of medicine, Johns Hopkins University School of Medicine and director, Allergy Clinic, Johns Hopkins Hospital With a foreword by Warfield R. Longcope, M.D., professor of medicine, Johns Hopkins University School of Medicine, and physician-in-chief, Johns Hopkins Hospital 8°, cloth, 334 pp, with 80 illustrations, 5 plates and 39 tables Baltimore Williams and Wilkins Company, 1946 \$5.00

REG Rheocardiography: A method of circulation's investigation and diagnosis of circular motion By W. Holzer, K. Pelzer, and A. Marko From the Nerve Clinic, the Physiologic Institute and the Pharmacologic Institute of the University of Vienna Translated by Mrs. Emma M. Kreidl 8°, paper, 43 pp, with 44 illustrations Vienna Wilhelm Maudsloch, 1946

The Differential Diagnosis of Jaundice By Leon Schiff, Ph.D., M.D., associate professor of medicine, Department of Internal Medicine, University of Cincinnati College of Medicine, and director, Gastric Laboratory, Cincinnati General Hospital 8°, cloth, 313 pp, with 38 illustrations Chicago Year Book Publishers, Incorporated, 1946 \$5.50

The Chest: A handbook of roentgen diagnosis By Leo G. Repler, M.D., professor and chief, Department of Radiology, University of Minnesota Medical School 8°, cloth, 352 pp, with 338 illustrations Chicago Year Book Publishers, Incorporated, 1946 \$6.50

Three Mother's Sons By Edward A. Strecker, M.D., Sc.D., LL.D. 8°, cloth, 220 pp Philadelphia J. B. Lippincott Company, 1946 \$2.75

A Manual of Tomography By M. Weinbren, B.Sc., M.R.C.S. (Eng.), L.R.C.P. (Eng.), F.F.R. (Lond.), D.M.R.E. (Camb.), adviser in radiology, Union Defence Force, and radiologist, Chamber of Mines Hospital, Johannesburg 4°, cloth, 270 pp, with 397 illustrations London H. K. Lewis and Co., Limited, 1946 5s 4s

Studies of Compulsive Drinkers Part I Case histories By Herman Wurtz, M.D., and Leonard R. Sillman, M.D. Part II Psychological test results By Florence Halpern, M.A. Edited by Jane F. Cushman, M.A., and Carney Landis, Ph.D. With a foreword by Nolan D. C. Lewis, M.D. 8°, paper, 90 pp. New Haven Hillhouse Press, 1946. \$1.00

Principles in Roentgen Study of the Chest By William Snow, M.D., director of radiology, Bronx Hospital, and roentgenologist-in-charge, Harlem Hospital, New York City 8°, cloth, 414 pp, with 508 illustrations Springfield, Illinois Charles C Thomas, 1946 \$10.00

Medical Research: A symposium Edited by Austin Smith, M.D. 8°, cloth, 169 pp, with 17 illustrations Philadelphia J. B. Lippincott Company, 1946 \$5.00

Unhappy Marriage and Divorce: A study of neurotic choice of marriage partners By Edmund Bergler, M.D. With an introduction by A. A. Brill, M.D. 8°, cloth, 167 pp New York International Universities Press, 1946 \$2.50

Acetaminol: A critical bibliographic review By Martin Gross, M.D., research assistant and assistant professor, Laboratory of Applied Physiology, Yale University School of Medicine With an introduction by Howard W. Haggard, M.D., director, Laboratory of Applied Physiology, Yale University School of Medicine 8°, cloth, 155 pp, with 8 illustrations New Haven Hillhouse Press, 1946 \$3.00

Narcotics and Drug Addiction By Erich Hesse, M.D. 8°, cloth, 219 pp New York Philosophical Library, 1946 \$3.75

The Biology of Schizophrenia By R. G. Hoskins, Ph.D., M.D., director of research, Memorial Foundation for Neuro-Endocrine Research, Harvard Medical School, and Worcester State Hospital 8°, cloth, 192 pp New York W. W. Norton and Company, Incorporated, 1946 \$2.75

Medical Education and the Changing Order By Raymond B. Allen, M.D., Ph.D., executive dean, Colleges of Dentistry, Medicine and Pharmacy, University of Illinois Chicago Studies of the Committee on Medicine and the Changing Order, New York Academy of Medicine. 8°, cloth, 142 pp New York The Commonwealth Fund, 1946 \$1.50

Renal Diseases By E. T. Bell, M.D., professor of pathology, University of Minnesota Medical School 8°, cloth, 434 pp, with 115 illustrations Philadelphia Lea and Febiger, 1946 \$7.00

Allergy in Theory and Practice By Robert A. Cooke, M.D., Sc.D., attending physician and director, Department of Allergy, Roosevelt Hospital, New York City In association with Horace S. Baldwin and others 8°, cloth, 572 pp, with a color plate Philadelphia W. B. Saunders Company, 1946 \$8.00

An Integrated Practice of Medicine By Harold Thomas Hyman, M.D. Four volumes and index volume 8°, cloth, 4131 pp, with 1184 illustrations, 305 in color and 319 diagnostic tables Philadelphia W. B. Saunders Company, 1946 \$50.00

The Anatomy of the Bronchial Tree: With special reference to the surgery of lung abscess By R. C. Brock, M.S. (Lond.), FRCS (Eng.), surgeon to Guy's Hospital, Brompton Hospital and E. M. S. Thoracic Surgical Centre 8°, cloth, 96 pp, with 142 illustrations New York Oxford University Press, 1946 \$12.00

Gastroenterology in General Practice By Louis Pelter, M.D., associate attending physician, Greenpoint Hospital, Brooklyn, associate visiting physician, Brooklyn Cancer Institute, and adjunct physician, Beth Moses Hospital, Brooklyn With the collaboration of Louis A. Held, M.D., attending roentgenologist, Beth Moses Hospital, Brooklyn With contributions from Alexander Lewitan, M.D., consulting roentgenologist, Norwegian Public Health Service, New York, and adjunct roentgenologist, Beth Israel Hospital, New York, Samuel Waldman, M.D., associate attending physician, Greenpoint Hospital, Brooklyn, and Siegfried W. Westing, M.D., roentgenologist, Brooklyn Cancer Institute 8°, cloth, 285 pp, with 108 illustrations and 15 tables Springfield, Illinois Charles C Thomas, 1946 \$7.50

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

NEW APPOINTMENTS

Victoria M. Cass, M.D., has been appointed epidemiologist in the Division of Administration, Massachusetts Department of Public Health. Dr. Cass held the position of teaching fellow in pathology at Tufts College Medical School from 1942 to 1944. Prior to her recent appointment, she was house officer, Medical Service, Boston City Hospital.

Joseph H. Hanson, M.D., formerly of the Medical Corps, A.U.S., has been appointed epidemiologist in the Division of Communicable Diseases, Massachusetts Department of Public Health.

Margaret M. Haehnel, M.S., has been appointed public-health social-work supervisor in the South Metropolitan District of the Massachusetts Department of Public Health. Mrs. Haehnel has been associated with the Worcester Children's Friend Society, the Family Welfare Society, of Springfield, and the Pondville Cancer Hospital.

Claire F. Ryder, M.D., formerly research resident and teaching fellow in tropical medicine at the Boston City Hospital, has been appointed epidemiologist in the Division of Administration, Massachusetts Department of Public Health. Prior to attending the Army Medical School in Washington, D.C., Dr. Ryder was house officer at the Boston City Hospital.

A. Geraldine White, A.B., has been appointed research consultant in the Child Growth and Development Program, Division of Maternal and Child Health, Massachusetts Department of Public Health. Miss White formerly held the position of health education assistant with the Middlesex Health Association.

Isah L. Salzman, M.S., who held the position of social worker with the Boston Department of Public Welfare, has been transferred to the Northeastern District of the Massachusetts Department of Public Health.

Brooks Ryder, M.D., a former captain in the Medical Corps, A.U.S., has been appointed epidemiologist in the Division of Local Health Administration, Massachusetts Department of Public Health. Prior to his appointment, Dr. Ryder was research assistant in anatomy at Tufts College Medical School. He served his internship at the Boston City Hospital.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Conduction Anesthesia. Clinical studies of George P. Pitkin, M.D. Edited by James L. Southworth, M.D., and Robert A. Hingson, M.D. 4°, cloth, 981 pp., with 606 illustrations. Philadelphia: J. B. Lippincott Company, 1946. \$18.00.

Modern Management in Clinical Medicine. By F. Kenne Albrecht, M.D., senior assistant surgeon, United States Public Health Service, and Kansas State Tuberculosis Consultant. 4°, cloth, 1238 pp., with 237 illustrations. Baltimore: Williams and Wilkins Company, 1946. \$10.00.

Intracranial Complications of Ear, Nose and Throat Infection. By Hans Brunner, M.D., associate professor of otology, University of Illinois College of Medicine. 8°, cloth, 444 pp., with 95 illustrations. Chicago: Year Book Publishers, Incorporated, 1946. \$6.75.

Anesthesia in General Practice. By Stuart C. Cullen, M.D., head of Division of Anesthesiology, Department of Surgery, State University of Iowa Hospitals, and associate professor of surgery (anesthesiology), State University of Iowa College of Medicine. 8°, cloth, 260 pp., with 36 illustrations and 4 tables. Chicago: Year Book Publishers, Incorporated, 1946. \$3.50.

Treatment of Bronchial Asthma. By Vincent J. Derbes, M.D., instructor in medicine and in preventive medicine, Tulane University of Louisiana School of Medicine, assistant visiting physician, Charity Hospital of Louisiana, and director of the Department of Allergy, Ochsner Clinic, and Hugo T. Engelhardt, M.D., instructor in clinical medicine, Baylor University College of Medicine, Houston, Texas, adjunct in medicine, Jefferson Davis Hospital, Houston, and visiting physician, Charity Hospital, New Orleans. With chapters by a panel of contributors. 8°, cloth, 466 pp., with 61 illustrations. Philadelphia: J. B. Lippincott Company, 1946. \$8.00.

Peptic Ulcer: Its diagnosis and treatment. By I. W. Held, M.D., attending physician, Beth Israel Hospital, and A. Allen Goldbloom, M.D., assistant clinical professor of medicine, New York Medical College and Flower and Fifth Avenue Hospitals, associate physician, Beth Israel and Metropolitan Hospitals, and associate cardiologist, Beth Israel Hospital, New York City. 8°, cloth, 383 pp., with 110 illustrations. Springfield, Illinois: Charles C. Thomas, 1946. \$6.50.

Shock Treatment and Other Somatic Procedures in Psychiatry. By Lothar B. Kalnowsky, M.D., research associate in psychiatry, Columbia University, College of Physicians and Surgeons, and New York State Psychiatric Institute and Hospital, and assistant neurologist, Neurological Institute of New York, and Paul H. Hoch, M.D., assistant clinical psychiatrist, New York State Psychiatric Institute and Hospital, and instructor in psychiatry, Columbia University College of Physicians and Surgeons. With a foreword by Nolan D. C. Lewis, M.D., professor of psychiatry, Columbia University College of Physicians and Surgeons, and director, New York State Psychiatric Institute and Hospital. 8°, cloth, 294 pp. New York: Grune and Stratton, 1946. \$4.50.

Clinical Methods of Neuro-ophthalmologic Examination. By Alfred Kestenbaum, M.D., assistant clinical professor of ophthalmology, New York University, lecturer in ophthalmology, Mt. Sinai Hospital, associate ophthalmologist, City Hospital, consultant ophthalmologist, Psychiatric Department, Bellevue Hospital, and Neurologic Department, Goldwater Memorial Hospital. 8°, cloth, 384 pp. New York: Grune and Stratton, 1946. \$6.75.

Early Ambulation and Related Procedures in Surgical Management. By Daniel J. Leithauser, M.D., chief of surgery, St. Joseph Mercy Hospital, Detroit. 8°, cloth, 232 pp., with 36 illustrations and 6 tables. Springfield, Illinois: Charles C. Thomas, 1946. \$4.50.

Practical Malariology. Prepared under the auspices of the Division of Medical Sciences, National Research Council, by Paul F. Russell, M.D., M.P.H., Parasitology Division, Army Medical School, Luther S. West, Ph.D., head of Biology Department, Northern Michigan College of Education, and Reginald D. Maxwell, Sc.D., professor of zoology, Syracuse University. 8°, cloth, 683 pp., with 238 illustrations. Philadelphia: W. B. Saunders Company, 1946. \$8.00.

The New England Journal of Medicine

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Volume 236

JUNE 19, 1947

Number 25

ANNUAL ORATION

MEDICAL CARE IN OUR FREE SOCIETY*

LELAND S. MCKITTRICK, M.D.†

BOSTON

The objective of adequate medical care in our free society is to make available to everyone — regardless of race, color, creed, financial status or place of residence — every known essential preventive, diagnostic and curative medical service of high quality. The attainment of such medical care must necessarily be an evolutionary process which will require the co-operation of all concerned over a period of years.

I have chosen as the subject of my oration this paragraph from the *Basic Principles Which Should Govern Medical-Care Plans*, which the Massachusetts Medical Society presented last year. Concise and complete, it stands as a challenge, if not a commitment, to us as members

Available to Everyone Regardless of Financial Status

Financial status as applied to medical care is a relative term. To the head of a household, modest but sound, the cost of an appendectomy for one of the children may be met without undue hardship. Should the head of this household suffer a long and tedious illness, the unavoidable financial obligations assumed may represent a burden that not only is a hardship but also may be overwhelming.

A consideration of the availability of medical care to the people of this Commonwealth must include a study of the income of the prospective recipients as well as of the cost of the services rendered. Interested in and busy with the calls of our patients, few of us have given thought to the earnings of the people of the Commonwealth that we as a profession serve.

It has been with much greater difficulty than would have been anticipated that information was obtained that might give us some reasonably accurate data on the relative number of workers in this state who fell into the different income classes.

Figure 1 is based on data compiled by the United States Treasury Department ‡

Whereas wages in 1942 were at a lower level than those of the present, the wage earners' income was probably higher because of overtime and other incentives used to increase production. To me, this is an impressive picture. It must be kept constantly in mind as we discuss the problem of a program that will make good medical care available to all the people of the Commonwealth.

Good medical care is and will remain expensive, but the continued rising costs of this care are a concern to us all. Yet there must be a ceiling to such costs, or else they cannot continue to be met by too large a segment of our population, and the price put on good health will be out of proportion to that on other necessities and privileges of our daily life.

As one might expect, most of the increasing costs are in hospital and nursing care. Thus, in 1940 the average total per-diem hospital charge, exclusive of professional and special nursing care, to 100 patients in the lowest price accommodation at the Baker Memorial Hospital was \$7.31, and in 1947 this same care cost the patient \$13.40 daily, or \$93.80 per week.

What are the factors responsible for this, and how are they being met? The financial problems of the voluntary hospitals were presented in a forceful and realistic way by Dr. Faxon* in his address at the Ether-Day Exercises last October. Two months later, the Hospital Council of Boston, after careful deliberation, recommended that the hospitals of the Greater Boston area adopt a pay-as-you-go philosophy for meeting rising costs and diminishing voluntary contributions. Specifically, the Council recommended that in the near future hospital rates be

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 20, 1947.

†Associate in surgery, Harvard Medical School; surgeon-in-chief, Palmer Memorial Hospital; surgeon, New England Deaconess Hospital; visiting surgeon, Massachusetts General Hospital.

‡The basis of the data is Table 8, which presents individual returns with net income for 1942 by taxable and nontaxable returns and by net income classes, and also aggregates by states for individual returns with no net income and for taxable fiduciary returns with net income.

The Ego and the Mechanisms of Defense By Anna Freud Translated from the German by Cecil Baines 12°, cloth, 196 pp., New York International Universities Press, Incorporated, 1946 \$4 00

Chronic Diseases and Psychological Invalidism A psychosomatic study By Jurgen Ruesch, M.D. With a foreword by Karl M. Bowman, M.D. From the Division of Psychiatry, University of California Medical School, and Langley Porter Clinic, San Francisco 8°, paper, 191 pp. New York American Society for Research in Psychosomatic Problems, 1946 \$3 00

Urgent Surgery Edited by Julius L. Spivack, M.D., associate professor of surgery, University of Illinois College of Medicine, senior attending surgeon, Columbus Memorial Hospital, Chicago, and attending surgeon, Oak Forest Infirmary Volume I 8°, cloth, 714 pp., with 244 illustrations Springfield, Illinois Charles C Thomas, 1946 \$10 00

Penicillin in Neurology By A. Earl Walker, M.D., associate professor of neurologic surgery, University of Chicago School of Medicine, and Herbert C. Johnson, M.D. resident neurologic surgeon, University of Chicago School of Medicine 8°, cloth, 202 pp., with 72 illustrations Springfield, Illinois Charles C Thomas, 1946 \$5 00

Psychiatric Interviews with Children Edited by Helen Leland Witmer 8°, cloth, 443 pp. New York The Commonwealth Fund, 1946 \$4 50

Personality of the Preschool Child The child's search for his self By Werner Wolff, professor of psychology, Bard College 8°, cloth, 341 pp., with 118 figures New York Grune and Stratton, 1946 \$5 00

Surgical Treatment of the Soft Tissues Edited by Frederic W. Bancroft, M.D., associate clinical professor of surgery, Columbia University, attending surgeon, New York City and Beth David hospitals, consulting surgeon, Veterans Administration, Lincoln and Harlem hospitals, New York City, and Kings Park State Hospital, Kings Park, New York, and George H. Humphreys, II, M.D., Sc.D., Valentine Mott Professor of Surgery, Columbia University College of Physicians and Surgeons, and director of Surgical Service, Presbyterian Hospital, New York City 4°, cloth, 520 pp., with 244 illustrations Philadelphia J. B. Lippincott Company, 1946 \$15 00

Adjustment to Physical Handicaps and Illness A survey of the social psychology of physique and disability By Roger G. Barker, Beatrice A. Wright and Mollie R. Gonick 8°, paper, 372 pp. New York Social Science Research Council, 1946 \$2 00

Radical Surgery in Advanced Abdominal Cancer By Alexander Brunschwig, M.D., professor of surgery, University of Chicago 8°, cloth, 324 pp., with 117 illustrations and 16 tables Chicago University of Chicago Press, 1947 \$7 50

Textbook for Psychiatric Attendants By Laura W. Fitzsimmons, R.N., B.S., M.A., assistant director of nurses and chief neuropsychiatric nurse, United States Veterans Administration, and chairman, Committee on Psychiatric Nursing, National League of Psychiatric Nursing 8°, cloth, 332 pp. New York Macmillan Company, 1946 \$3 50

Diagnosis and Treatment of Menstrual Disorders and Sterility By Charles Mazer, M.D., assistant professor of gynecology and obstetrics, Graduate School of Medicine, University of Pennsylvania, and gynecologist, Mount Sinai Hospital, Philadelphia, and S. Leon Israel, M.D., instructor in gynecology and obstetrics, University of Pennsylvania School of Medicine, and associate gynecologist, Mount Sinai Hospital, Philadelphia Second edition revised and enlarged 8°, cloth, 570 pp., with 133 illustrations New York Paul B. Hoeber, Incorporated 1946 \$7 50

Radiology for Medical Students By Fred J. Hodges, M.D. professor and chairman, Department of Roentgenology University of Michigan Medical School, Isadore Lampe M.D., associate professor, Department of Roentgenology University of Michigan Medical School, and John F. Holt M.D., assistant professor, Department of Roentgenology University of Michigan Medical School 8°, cloth, 424 pp., with 103 plates Chicago Year Book Publishers, Incorporated, 1947 \$6 75

Adolescent Sterility A study in the comparative physiology of the infecundity of the adolescent organism in mammals and man By M. F. Ashley Montague, associate professor of anatomy, Hahnemann Medical College and Hospital, Philadelphia, and visiting lecturer, Department of Sociology, Harvard University 8°, cloth, 148 pp., with 33 tables Springfield, Illinois Charles C Thomas, 1946 \$3 50

Penicillin in Syphilis By Joseph E. Moore, M.D., associate professor of medicine and adjunct professor of public-health administration, Johns Hopkins University School of Medicine, physician-in-charge, Syphilis Division of the Medical Clinic, and visiting physician, Johns Hopkins Hospital, chairman, Syphilis Study Section, National Institute of Health, United States Public Health Service, and chairman, Subcommittee on Venereal Diseases, National Research Council 8°, cloth, 319 pp., with 57 illustrations and 52 tables Springfield, Illinois Charles C Thomas, 1946 \$5 00

Military Neuropsychiatry Proceedings of the Association for Research in Nervous and Mental Diseases Volume XXV 8°, cloth, 366 pp. Baltimore Williams and Wilkins Company, 1946 \$6 00

Postgraduate Obstetrics By William F. Mengert, professor and chairman, Department of Obstetrics and Gynecology, Southwestern Medical College, and chairman, Obstetrics and Gynecology, Parkland Hospital, Dallas, Texas 8°, cloth, 392 pp., with 123 illustrations New York Paul B. Hoeber, Incorporated, 1946 \$5 00

Uterine Contractility in Pregnancy A study of the contractions of pregnancy and labor under normal and experimental conditions By Douglas P. Murphy, M.D., assistant professor of obstetrics and gynecology and research associate in the Gynececan Hospital Institute of Gynecologic Research, University of Pennsylvania School of Medicine 4°, cloth, 134 pp., with 64 illustrations Philadelphia J. B. Lippincott Company, 1946 \$5 00

NOTICES

RESIDENCY IN RADIOLOGY

Applications will be considered for appointment to a residency in radiology at the Joseph H. Pratt Diagnostic Hospital and Boston Dispensary from physicians with one or two years of training in radiology. There are about 1800 diagnostic cases monthly, as well as a tumor clinic and therapy and teaching conferences. Appointments will be made for one year beginning September 1, 1947.

Applications should be addressed to Mr. Richard T. Viguers, administrator, Joseph H. Pratt Diagnostic Hospital, 30 Bennet Street, Boston 11.

SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the Prendergast Preventorium, 1000 Harvard Street, Mattapan, on Tuesday, June 24, at twelve noon. Dr. Eli Friedman will speak on the subject "Some Interesting Problems in Pediatrics."

This meeting will mark the twentieth anniversary of the Club.

(Notices continued on page xix)

mouth until there is stabilization of all labor at a more nearly normal level. We are greatly concerned, however, over the increasing demands for and the rising costs of nursing and over how these are to be met in the future. There must be and there is a solution to these needs, which can and will be worked out by a carefully planned and executed program and which has as its incentive one objective — the welfare of the patient rather than the continuation or extension of any existing patterns. Thus, there is much reason to believe that the present three years' training program leading to the R N degree is unnecessarily long and costly for preparing a young woman to carry out a large segment of bedside care, and that it is not adequate to develop a truly professional teaching and supervising personnel of high quality. Some breakdown, then, of our present concept of nursing care may be necessary. Just what pattern shall be followed may well depend on such experiments as are being carried out at present at the Massachusetts General Hospital, where a group of "earn-as-you-learn" hospital aids are being used under careful supervision for the routine bedside care of patients on two of the surgical wards. Possibly, as has been suggested, we should have three groups involved in our hospital nursing services: first and probably largest, young women and men trained for relatively short periods — probably not to exceed one year — to carry the burden of routine bedside care, secondly, young women and men with an adequate but not overscientific background trained to care for the more complicated and critically ill patients — a training that quite possibly might be condensed into less than the present three-year period, and finally, a group of truly professionally minded and trained young women, whose responsibilities will be the supervision of our wards, the development of nursing programs and the teaching of the nursing personnel at all levels.

It is believed by many that 60 per cent or more of bedside nursing can be done by young women and men with the relatively short period of training. Whereas the more complicated operations such as those on the thoracic viscera and the brain are being done in increasing numbers and require constant and skilled nursing, the care of routine general surgical patients (and, I suspect, of medical patients too) has been simplified, not complicated, by recent developments. What so many of these patients need for a few days is attention, not complicated professional care. If this is true and if, as many experienced physicians believe, the bulk of routine patient care can be done by young women after short periods of training, is it not conceivable that by lowering the over-all cost of caring for the uncomplicated hospital patients and increasing the coverage given to those critically ill, a concept of hospital care could be developed, the cost of which to the individual would be well below that of the present plan if one includes the almost routine use

of special-duty nurses, when they are available, in the early days following operation? But whatever method may be developed, surely at least a part of the high cost of hospital care must be met by a changing concept of what hospital service means to the patient seeking and paying for it.

An important, if not the most important, factor in the development and final success of any plan conceived and adopted by hospitals for the more efficient and less costly care of sick patients will depend on the interest and co-operation of the medical profession. Who, for example, shall decide whether a patient requires special attention or not? Surely not the hospital administration alone. You, the physician, better than anybody else know the condition of each patient, and extra services to those patients (exclusive of the luxury group) must be determined not on the wishes of patients or their families but on the condition of those patients in relation to the routine service that your hospital is able to give. Therefore, with the changing concept of what is best and most efficient for the care of our patients, let us take an active, aggressive and co-operative part in the development and execution of any constructive program that our hospitals may choose to establish.

Better routine care to the uncomplicated case with complete care to the seriously ill at the lowest possible cost that is spread among all patients entering the hospital in ward and semiprivate beds is, I believe, the objective toward which we should work.

But more inclusive and complete hospital service at the established rate is but a part of the answer. The over-all cost of good medical care will always be high, — too high for 84 per cent of the people of this Commonwealth to pay for out of pocket when the ax falls, — and it would be unfortunate indeed if any member of this Society failed to accept this as an integral part of his basic thinking. When you have accepted this, the inevitable question of compulsory versus voluntary coverage follows. There never has been and there is now no controversy between most of the proponents of the two methods over the objective, but there is complete divergence of opinion concerning the method by which that objective can most satisfactorily be reached. No one of you, nor I, nor anyone at this time has the vision to look into the future and say, "This or that is *the* method of paying for and distributing to the people of this country the highest possible quality of medical care." Whether we have voluntary or compulsory insurance will not of necessity depend on which is the better method but rather on what the people want. What the people want will depend on what proponents of a given method tell them as compared to how we as physicians lead and serve them. The proponents of compulsory insurance are now devoid of any favorable comparison. Medicine in England and Germany long ago ceased to favor it. Selective Service

established at such a level that they would approximate the cost of hospital care and suggested that in this community a rate of \$8 a day plus extras, or a total of about \$11 per day, be established as the minimum ward rate, with the understanding that those unable to pay the established rate be admitted as before for whatever they could pay. These rates were promptly accepted by most of the hospitals in the Boston area. If special nursing and professional fees are added to the \$11 or more a day and it is considered that in 1942, when earnings

fees used for this purpose. The results of these investigations benefit all prospective patients, not only in the hospitals in which the work is done but also in and out of all hospitals everywhere. The organization and execution of this work is the responsibility of teaching hospitals with adequate and well organized personnel and physical facilities. The financial responsibility in the past has been almost wholly assumed by private benefactors. Ideal as it is, this source is uncertain and is becoming more and more limited. Additional, more dependable sources (including federal funds) must be and are being sought and obtained. Although such money may well be given for a specific project, these grants should and must be complete and free from all obligations—moral or otherwise. At the same time, it is incumbent on these institutions to review their organizations and to be in a position to assure prospective donors that money so received is being used with the greatest possible efficiency—lest too much of what is available go into reduplication of effort, disorganized investigation and ill conceived and overlapping laboratory expenditures. Research well organized and efficiently done must continue to develop for the benefit but not at the expense of the sick patient alone.

Patient care, on the other hand, is the responsibility of the persons requiring hospital care and of the communities in which they live. If this is true and if in the future our voluntary private hospitals are to be supported by those who use them, is it not proper to ask whether or not our present hospital services are economical, efficient and a pattern to follow in future planning? In other words, what are the responsibilities of the hospital to the patients it accepts and now charges full payment for services rendered? Where do special nurses at \$25 or more a day fit into a program of such hospital care? Should they continue to be desirable for most patients undergoing routine major operations, even though in many of these cases their value to the patient and to the surgeon is in the constant attention to simple details in contrast to the experience, training and skill essential to the care of the more complicated conditions and the critically ill patients? Should special-duty nurses, as we now know them, offer a purely luxury service, except in cases in which they are assigned and paid for by the hospital to give the complete coverage that is necessary for the more seriously ill patients? Has not the time come when our concept of hospital service to the patients in semiprivate and ward accommodations requires careful and thorough revision and the adoption of a long-range program that will spread the cost of this care, regardless of the amount involved, over all patients entering the hospital?

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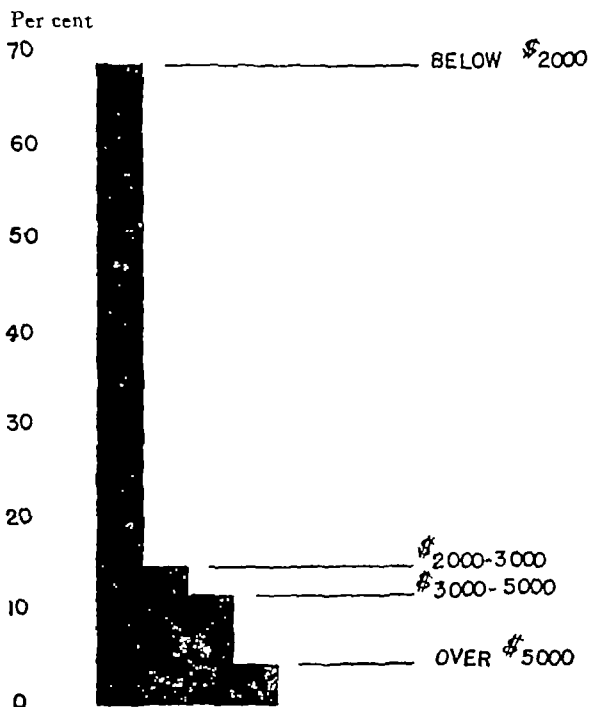


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and that there is substitution of all labor at a reasonably normal level. We are greatly concerned over the increasing demands for and the increasing cost of nursing and over how these are to be met in the future. There must be and there is a substitution of personnel which can and will be worked out in a carefully planned and executed program and such as its incentive and objective — the welfare of the patient rather than the continuation of personnel of any existing patterns. Thus, there is no reason to believe that the present three years' training program leading to the R.N. degree is unnecessarily long and costly for preparing a young woman to carry out a large segment of bedside care, and that it is not adequate to develop a truly professional training and supervising personnel of high caliber. Some breakdown, then, of our present concept of nursing care may be necessary. Just what pattern shall be followed may well depend on such experiments as are being carried out at present at the Massachusetts General Hospital, where a group of "learn-to-learn" hospital aides are being used under careful supervision for the routine bedside care of patients on two of the surgical wards. Possibly, as has been suggested, we should have three groups involved in our hospital nursing services — first and probably largest, young women and men trained for relatively short periods — probably not longer than one year — to carry the burden of routine bedside care, secondly, young women and men with an adequate but not over-scientific background trained to care for the more complicated and critical ill patients — a training that quite possibly might be condensed into less than the present three-year period, and finally, a group of truly professional-minded and trained young women whose responsibilities will be the supervision of our wards, the development of nursing programs and the teaching of the nursing personnel at all levels.

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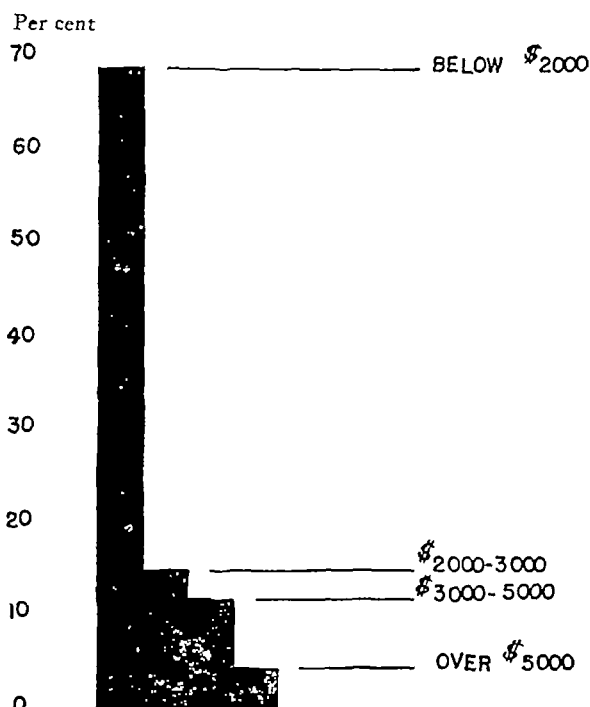


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statistics have been debunked. The United States Public Health Service, long cited as a Government agency efficiently run and free from any political pressure, fell from grace when each of its officers, including those in the Reserve,² was instructed by the Surgeon General of the Service³ to familiarize himself with the President's message (September 6, 1945) and to be guided by its provisions in any "public statement likely to be interpreted as representing the official views of the Public Health Service." And the public school, so often referred to as representing a form of taxation effectively returned to the people as public education, is no longer pointed to as an example of the efficiency and flexibility with which Government meets changing economic conditions. Devoid, then, of examples, the proponents must depend on theory, organization, propaganda and promises. But do not underestimate the logic of compulsory health insurance. In theory, on paper or over the air, it has everything. You and I, as practicing physicians, know that the problem is anything but as simple as Mr. Falk, Senator Pepper and others would have us believe. Not only do we as a group deliver to the people of this Commonwealth the greater part of their medical care, but also we, better than anyone else, know the problems. We know what keeps us on telephone call and what gets us out in the middle of the night, as well as what the people want, need and have a right to expect of their doctor. If this is true, should it not be possible for us to do our job as physicians and, in addition, to convince the people we serve, not only by valid argument but also by the effectiveness and sincerity of our efforts in their behalf? Are we not, by example, in a better position to reach the people of our community than those who must depend on words and promises alone?

We can be grateful to the Council of the Society for its wisdom and foresight in setting up the medical-care program as expressed through the Blue Shield. It is gratifying to learn that two million, or 50 per cent, of the residents of Massachusetts are now enrolled in Blue Cross and that Blue Shield had increased its membership by 108 per cent from January 1, 1946, to January 1, 1947. Both are to be congratulated on their rapid growth and their new comprehensive plans, effective on June 1, 1947, whereas there are some controversial points in the new Blue Cross coverage, these can and will be satisfactorily adjusted. It might not be amiss, however, to remind the directors of these services that they are a necessity for 84 per cent of the wage earners of this Commonwealth, but only a convenience to the remaining 16 per cent, and that any pressure from or desire to increase the appeal to the latter must not result in excessive cost to those they have been created to serve. These services must continue to grow and develop. Unless we as physicians have constantly before us the best interests of the people of Massachusetts

and do our utmost individually and collectively to make possible better and better care through individual efforts and an aggressive, co-operative medical-care program, we shall have failed not only in our duty but also in our opportunity. The time is past when any but the well-to-do can pay for a serious hospital illness when or after sickness occurs. Prepayment for hospital and medical care for the people of this Commonwealth is here to remain. Whether it continues to expand and progress and to develop on a voluntary basis with its many possibilities or whether it is ultimately placed on a compulsory basis with its inefficiency and governmental regulation is up to us.

Regardless of Financial Status

There is a large group in this, as in every state, who can pay for little or no part of its medical care. It will vary in size, depending on economic conditions and other factors. This is a large and an important group, and provision for its care is, according to our principles, the responsibility of the local or state government with the help of charitable agencies and if necessary federal grants-in-aid to state programs. Many are honest, frugal people who pay their normal way but have no savings or no prospects for meeting abnormal expenses. Others have never met and will never meet any obligations. A medical-care program that does not include this group is not complete and will not permanently survive.

Every Known Essential Preventive Diagnostic and Curative Medical Service of High Quality

Prevention of disease is the first fundamental of good medical care. The Commonwealth is favored with a public-health department of unusually high quality. To Massachusetts in 1869 went the honor of establishing the first state department of health in this country. In spite of its seventy-eight years of progress and its excellent record, however, over half the citizens of the Commonwealth are deprived of the benefits of the latest developments of medical science and preventive medicine.⁴ Until all the communities in the Commonwealth are covered with full-time medical health officers with special training in public-health work, until such men are given adequate compensation and until there is real co-ordination in all the public-health work of the Commonwealth at both state and local levels, preventive medical service of high quality will not be available to all the people of Massachusetts.*

Diagnostic and curative medical care go hand in hand. Far too much has been said in recent years about the cost and distribution of medical care, and much too little about the quality of services given. Both are important. Both must be developed. But unless the quality of service given

*Every member of the Society is urged to read the excellent survey of the program of the Department of Health referred to above.

is constantly improved, its distribution and the methods of paying for it are of little significance. You and I, who in the past have thought largely in terms of doing our daily work to the best of our ability, must now give thought not only to our patients but also to the organization and the development of our hospital and professional facilities to provide medical services of higher and higher quality, as well as to the development of organizations that make these services available to all the people of our communities. Fewer patients should come to our larger cities for care that can and should be given in their own community.

What, then, are the most important factors in a medical-care program whose object is to offer to a given community the best possible medical service, and what are our responsibilities as physicians in the development and utilization of these various factors?

A modern hospital of adequate size with an active, effective and co-operative governing board and an able, well organized professional staff are essential for a medical-care program of high quality.

Completely to fulfill its place in the community, the hospital must be the center of health activities. It is not enough that this hospital is of modern construction, well equipped and soundly financed. It must, in addition, be of sufficient size, preferably two hundred beds or more, although in many communities excellent, if more limited, medical and surgical services are being offered in smaller units. With few exceptions, however, hospitals with less than two hundred beds are dependent on larger institutions or outside personnel for many of the services essential to diagnosis and treatment of even the more frequent conditions. Also, the smaller the hospital, the more limited the staff and its clinical experience.

It has been suggested that a hospital of approximately two hundred beds can be efficiently maintained and offers sufficient clinical and laboratory material to assure well trained full-time radiologic, pathological and laboratory personnel. Moreover, the number of patients cared for is adequate to attract young men of ability and with proper training to assure a professional staff of high quality. I see little justification for the erection of general hospitals of fewer than two hundred beds except in rural areas, of which in this Commonwealth there are relatively few. How much better to follow the lead of the people of Newton and Wellesley and have adjacent communities join in the erection and maintenance of a plant of adequate size to be completely self-supporting and self-sustaining!

The trustees or governing bodies of our hospitals have a broader responsibility than the building and maintaining of the physical plant. One may well ask whether or not such a board is justified in urging a community to raise a large sum of money to erect and equip a modern hospital unless it is

prepared to support, to encourage or, if necessary, to insist on the development of a staff organization that will assure a quality of care in keeping with the institution to be built and supported. There is too often lack of co-operation between the trustees and the professional staff. Only by continued exposure of each to the problems of the other can there be proper understanding. Without this, no lay person, no matter what his interests, can appreciate the many practical problems of the physician in the care of his patients, and only by a better understanding and closer co-operation between trustees and staff will it be possible for modern hospitals to function with their greatest efficiency.

Given proper facilities in which to work and a responsible, co-operative governing board, the quality of medical care is dependent on — in fact, is — the complete responsibility of the medical staff. We share with no one the training and experience necessary to develop for the people of our communities the high type of medical care to which they are entitled. Our American way of free enterprise has placed high award on individual initiative. Medicine, by its very nature, has encouraged in every way the development of the individual instincts in all of us. No one can ever criticize the great mass of American physicians for any lack of personal application to their professional work. But the many advances in medical knowledge and the increasing complexity of medical care require more than individual application if patients are to be assured of the best possible care. Medical care of high quality is the end product of combined and well co-ordinated efforts. It has as its objective the welfare of the community as a whole, as well as of the individuals within the community. What is for their benefit will prove to be to our interests. It is no longer possible for anyone — no matter how capable, well trained or conscientious — to give complete medical care to any segment of his community, nor is it necessary that he try in so enlightened a state as ours. The co-ordination of individual efforts through group organization or within the well organized staffs of our community hospitals is, then, the guide to our professional development.

In the great proving ground of America, group medical care of every kind has been highly developed and is being successfully carried out. It remains for us in our various communities to select and develop the particular type that best suits our needs. Whatever the pattern, whether it be as a closely organized specialty group as exemplified in this community by the Lahey Clinic, or whether it be the more frequent, loosely knit organization of the entire professional staff around its hospital, as probably most highly developed in the Commonwealth at the Baker Memorial Hospital, there are certain requirements that are essential. It must offer the development of major and, when possible,

minor specialties, with the head of each department certificated by his respective board, recognition of and encouragement to general practitioners (except in certain specialty and teaching hospitals), assurance of a continuing high quality of care through the institution and development of a teaching program, and facilities for and frequent use of unrestricted consultations

The development of an effective staff organization (and for the moment I will restrict my comments to the surgical staff) that will attract well trained young men to our communities, assure them of an opportunity to develop and co-operate in the medical-care program and utilize the established personnel but at the same time develop a spirit of pride in and loyalty to the hospital and through it to the people of the community, rather than one of ownership in and jealousy of the hospital privileges that they enjoy, is a truly challenging responsibility. The people of this Commonwealth owe much to the hundreds of excellent surgeons who have learned surgery by long and continued application over the hard road of experience. Without them, surgery could not possibly have developed to its present high standard, and thousands of people in this Commonwealth would have been denied the relief that has been theirs through the untiring work of these men. But the advances in surgery over the twenty-eight years that I have been a member of this Society beggar our imagination. No body cavity, no viscus, is exempt from safe surgical approach. Resections of the stomach, colon or rectum are now carried out by our senior resident staff with a competence and safety that even ten years ago we should have thought neither practical nor possible. These advances have not just appeared. They are the result of continuous study and application of men in our teaching hospitals and their laboratories in co-operation with the laboratories of our medical schools. There have evolved new principles and a more thorough understanding of the old. Surgery has become too complicated, too all-inclusive for a young man to learn as a part of his daily medical practice or solely by association with an older man. The surgeon of tomorrow will be trained in the larger teaching hospitals of today and in the institutions that are developed tomorrow. Only by continued study and limitation of all his thoughts and efforts to the work of his choice can the surgeon of the coming generation expect and receive recognition by the governing boards of the hospitals in our larger communities. This generation of surgeons must be carefully trained in our hospitals under experienced supervision. Only in recent years have any of our hospitals, even the large teaching institutions in Boston, given sufficient training to qualify their graduates to do surgery in their own right. This is now being well done in many of our larger teaching hospitals throughout the country, but more opportunities are needed for

young men anxious to give time and effort for a sound surgical training. The development of proper staff organization in the larger general hospitals of this Commonwealth not only will offer more opportunities for a new generation of surgeons but also will assure the patients in those hospitals of the high quality of professional care that goes with a resident program.

Organization of the hospital staff into the several specialties, each headed by a man certificated by the specialty board, interested in and willing to give enough of his time and effort to the development of his department, restriction of staff members to those limiting their work to their own specialty and the establishment of a merit system whereby appointments to and promotion of the staff are made on a basis of ability and application rather than seniority are the first steps in assuring professional care of the highest possible quality and to the later introduction of a resident program. I should add that, at least for the present, I consider it neither necessary nor desirable for a hospital to require that all its staff members be either certificated by their specialty boards or that those on the surgical staff be fellows of the American College of Surgeons. Insistence on these credentials will not in itself assure good care and is certain to prove a hardship to many able men who by years of application are capable of and are doing excellent work in their communities. Ability, application and a progressive and active interest in the continued development of the medical-care program rather than diplomas on the wall should be the basis for appointment to the staff of our community hospitals. I do believe, however, that all heads of departments and men holding senior staff positions should be certificated by their boards and that the surgeons in more responsible positions should be fellows of the American College of Surgeons.

Any staff organization that does not recognize and include the general practitioners of the community that the hospital serves is not giving full service to that community. There are those who have said that the days of the general practitioner are gone, but the general practitioner has been, is now and will continue to be the real backbone of our medical-care program. The American Medical Association has recognized this in the establishment of a Section of General Practice, and it is probably only a matter of a short time before there will be a specialty board to certificate men in general practice as well as men in the various specialties. They are an intimate part of medical care in any community and must therefore be an active part of the staff organization of all except the highly specialized or the large teaching hospitals.

Closely associated with the staff organization is the development of a teaching program without which no hospital staff can continue to fulfill its complete obligations to the community. Teaching at

some level is possible in every well organized institution. Teaching will be most effectively done and at its best if there are active young minds attached to the hospital as part of a training program. Even without interns or residents, however, hospital clinics, clinicopathological exercises and other scientific programs can and must go on continuously to stimulate the thinking and reading of the staff members and to assure to all patients of the community the benefits of the newer trends in medicine.

What about research? Let us never forget that all medical education and all investigative work have as their ultimate objective the improvement of the medical care of people who need it. Unless new discoveries can find clinical application, they are of little or no importance. One of the really great problems in American medicine lies in the practical application of what we learn to the people of the communities we serve. The possibilities for real constructive advances in the development of medical services in the hospitals of this Commonwealth are almost limitless. That many of even the common medical and surgical cases still come to our larger cities is a natural result of the concentration of the more highly trained internists and surgeons in those areas. As more young men are well trained in the various specialties, however, the trend in medical care for all but the more complicated conditions must be from our larger metropolitan teaching centers back to the communities in which the patients live. The opportunities for men with imagination to develop sound, workable programs in our community hospitals that will make this possible offers a challenge equal to that of the teaching hospital and its laboratories.

Probably one of the most important contributions of good staff organization and co-operation comes from the free exchange of knowledge through frequent use of consultations. These consultations, to be truly effective, must be unrestricted and must make use of any member of the hospital staff, or if necessary of the staff of a neighboring hospital, who can give the greatest help toward the solution of a given patient's problem. In no small degree, the excellence of care given in any one of our hospitals is reflected in the degree to which the consultation service utilizes the knowledge and experience of the entire professional and laboratory staff.

Available to Everyone — Regardless of Race, Color, Creed, Financial Status or Place of Residence — Every Known Essential Preventive, Diagnostic and Curative Medical Service of High Quality

To make medical care available to all the people of the Commonwealth, 84 per cent of whose net

weekly income is below \$60, when the cost of a ward or semiprivate bed in a Boston hospital (exclusive of the cost of special nurses and professional care) varies from \$80 to \$90 a week, is a challenging undertaking. In addition to a mechanism of providing for those who cannot pay for themselves and of obtaining more complete prepayment coverage of the remainder of this group, careful re-evaluation of our present pattern of hospital care should be undertaken so that when economic conditions permit, hospital services may be altered to allow complete coverage to the patient in a ward or semiaccommodation at the lowest possible cost to the hospital and patient, with this cost shared by all patients, whether actual or potential recipients of total service, and paid for through membership in a voluntary prepayment plan. Accomplishment of this goal can be possible only if there is thoughtful, aggressive, co-operative effort of the public, the medical profession, the hospital and nursing authorities, our voluntary medical and hospital services, our charitable agencies and the local and state government units.

To assure continuing improvement of the quality of medical care requires additional effort by and co-operation between hospital governing boards and the professional staff. A well run hospital of adequate size with an effective staff organization, a teaching program and finally the development of resident training will offer to its community a quality of service of which it can be justly proud.

You and I have the good fortune to live at a time and in a state when what should be can be — but only if we as individuals as well as a society offer the active far-sighted leadership and the co-operation with other agencies that are so essential to success.

The attainment of such medical care must necessarily be an evolutionary process which will require the co-operation of all concerned over a period of years.

Addendum I am indebted to those innumerable and stimulating committee meetings, conferences, personal discussions and communications from which I have learned and to which I owe so much.

REFERENCES

- 1 *Basic Principles Which Should Govern Medical Care Plans* 7 pp. Massachusetts Medical Society Feb 6 1946
- 2 Faxon N W. Voluntary hospital — how can it survive in modern world? *Am Eng J Med* 236 460-464 1947
- 3 Mimeographed letter dated December 10 1945 to all officers of the Public Health Service (Subject: The National Health Program) From Thomas Parran Surgeon General United States Public Health Service
- 4 Getting Vlado A. Commonwealth's health program. *Am Eng J Med* 236 626-629 1947

THROMBOPHLEBITIS—THE PROBLEM OF TREATMENT*

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MUCH has been done by members of the New England Surgical Society and their associates leading to greater understanding of thromboembolism. A recent thorough and searching review by Homans¹ is classic in its contribution both to the student and to the clinician responsible to his patient. In the light of this and with exceeding deference, some of the problems arising in the approach to the patient with acute thrombosis of the deep veins of the extremities are discussed. The widespread consideration of this problem from many points of view attests to the uncertainty concerning any single most effective method of treatment.

There is general agreement regarding vigorous prophylaxis to maintain muscular tone and circulatory efficiency. Ochsner² stops his patients from smoking ten days before operation, applies compression bandages from ankle to groin and routinely employs dry heat to the abdomen and not to the extremities, to lessen peripheral vasospasm. Gentle operative technic without overmanipulation of the viscera and avoidance of surgery during the menstrual period find general acceptance. Postoperative elevation of the foot of the bed for forty-eight hours has been favored to aid in emptying the veins of the extremities. Most surgeons encourage their patients to wiggle their toes a thousand times three times daily, to leg movements every three to five minutes and to bicycle exercises. Many practice early rising, which has been termed "early ambulation."

Early ambulation may prove to be helpful. It should not be permitted to prove harmful. Allowing especially the elderly or debilitated patient to sit with the legs hanging in a flaccid dependent position, crossed or uncrossed, is not early ambulation. It is my opinion that the postoperative patient should either walk upright or remain lying in bed, being allowed up in a chair only when he is able to walk to it. Exercise of the leg muscles should be practiced while the patient is sitting. An increase in the frequency of headache following spinal anesthesia has caused me usually to defer early rising until at least forty-eight hours after operation.

In the care of the patient with signs of obstructive deep phlebitis of the extremities, the risk of embolism, however slight, is recognized early. A feeling of increased resistance of the tissues has proved a helpful sign, along with slight swelling and Homans's dorsiflexion sign. Bauer,³ from a large experience, advises early phlebography as routine in

all cases of suspected thrombosis, on the vaguest chest or local signs. Suggestive chest signs of infarction, of course, increase the urgency of decision regarding the method of treatment.

Little reliance should be placed on any attempt to differentiate a nonadherent and an adherent clot. Both have been observed in the same vein on several occasions. In 5 patients with femoroiliac thrombosis an adherent femoral thrombus, with proximal nonadherent grape-jelly clot in the iliac veins, was observed.

Most authorities agree that early and frequent use of sympathetic blocks with novocain throughout the period of pain, tenderness, fever and swelling may prove helpful. Injection of 10 cc of 1 per cent novocain into the region of the first, second, third and fourth lumbar sympathetic ganglions unilaterally or bilaterally has been employed, 100 cc of 1 per cent novocain being recognized as the accepted toxic dose. Tulane's young graduates practiced this with frequency in Army wards, as a result of Ochsner's insistence that every student be familiar with the indications for and easy execution of this as a ward procedure.

Decision should be made early—within the first twenty-four hours—concerning the major course of treatment, whether anticoagulants or proximal-vein ligation, or both, are employed. Attention should then be directed to the possibly helpful use of adjuvant measures, not only to safeguard against embolism but also to protect the collateral channels against spread of the thrombophlebitic process. A cradle with a light over the abdomen, abstention from smoking and sympathetic novocain blocks on the obstructed side, in addition to the equivocal effect of papaverine, may lessen vasospasm. Early exercise and post-ligation use of heparin or dicoumarol may further aid in quicker subsidence of the inflammatory process and may lessen the late effect on circulatory efficiency. Smithwick⁴ has suggested that in his experience sympathetic novocain block in the heparinized patient seems to produce increased effect.

If anticoagulant therapy is decided on, in the light of many published favorable experiences with both heparin and dicoumarol,^{5,6} certain facts should be kept in mind. Sustained vigilance of the unstable clotting times is essential for several days. With heparin the venous clotting time, checked twice daily to maintain an optimum time of between thirty and forty-five minutes, was observed to rise quickly to two and a half hours, fortunately with no ill effects. Both heparin and dicoumarol should be

*Presented at the annual meeting of the New England Surgical Society, Worcester, Massachusetts, October 4, 1946.

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used with extreme care in wounds involving the cranial, pleural and abdominal cavities and in fractures encased in plaster. Hematuria and hemorrhage into joints have been reported as untoward effects.³ Heparin clears from the blood quickly, within two or three hours. Dicoumarol produces no effect on the clotting time until the prothrombin level has been reduced to 30 per cent of normal.⁶ It requires two or three days to become effective, and loses its effect on the prothrombin level slowly. Properly administered, both heparin and dicoumarol seem un-

done relatively late in the disease, — ten days to several weeks after battle injury, — required ligation of the common iliac vein on the involved side, with supplementary ligation of the superficial femoral vein on the apparently uninvolved side. The remaining 4 cases developed during the hospital stay. Chest symptoms and signs or x-ray findings suggestive of pulmonary infarction were present in 6 cases. Bilateral ligation was done in 5 cases, and unilateral in 4. Additional measures in conjunction with ligation were used too meagerly, in retrospect

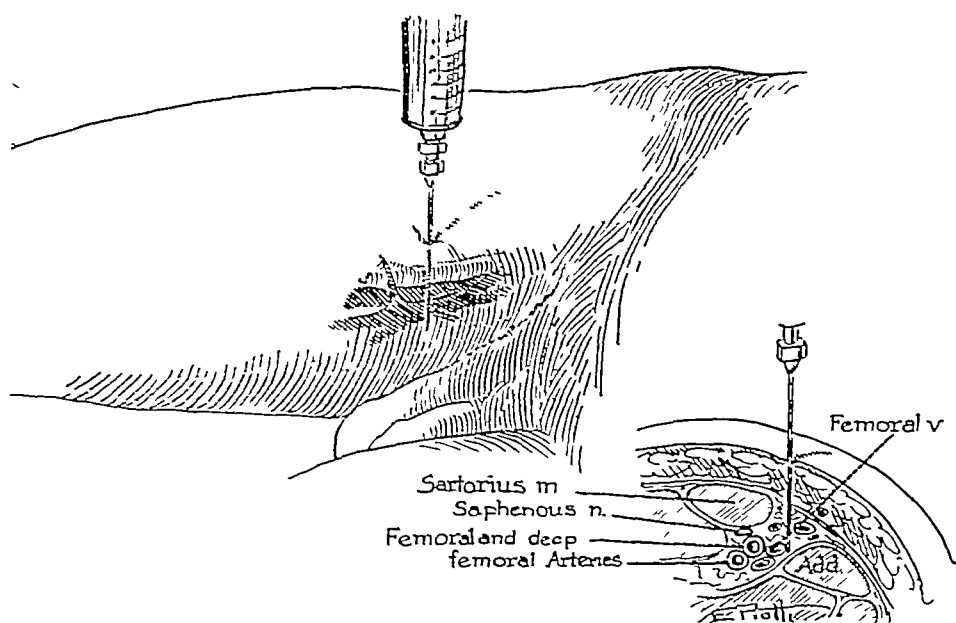


FIGURE 1 *The Vertical Injection of Novocain about the Great Femoral Vessel*

doubtedly effective despite the still obscure mechanism of their control of the formed clot.

When ligation of the involved or suspected veins has been decided on, every effort should be made toward early ligation. This may avoid the more drastic ligations at higher levels and should reduce the real frequency and severity of postoperative swelling, which still limits somewhat the acceptance of this procedure.

In an experience with 8000 patients in a fixed Army general hospital in England during the eleven months from D Day (June 6, 1944) to VE Day (May 11, 1945), 9 patients were subjected to proximal ligations at levels higher than the superficial femoral vein. Interest was stimulated toward ligation as the safest method of control, not only on the basis of civilian experience but also on autopsy observation on 2 soldiers in whom embolus had plugged the pulmonary arteries, with a truncated adherent thrombus in the right internal iliac vein in one patient and in the left common femoral vein in the other.

All nine patients had demonstrable obstructive thrombophlebitis. Five operations, which were

Heparin was used intravenously in only 3 patients, and lumbar sympathetic blocks with novocain in 2.

Although caution should be emphasized in the impressions gained from a few cases in such young patients, ranging from nineteen to thirty-six years of age, it may be stated that no further pulmonary disturbances developed, no untoward results were noted (except for nonincapacitating edema in 2 patients), and all patients, both in and out of leg casts, were allowed out of bed much earlier than they would have been without ligation. Follow-up letters seventeen months after these studies have revealed no additional sequelae.

The anesthesia employed was local in 4 patients at the level of the common femoral vein, and general in the 5 cases of iliac ligation (spinal anesthesia in 3, and ether in 2).

Certain technical features of ligation seem worthy of mention. Signs of pulmonary infarction or of phlebitis of the pelvic veins impel one to ligate at the level of the common femoral and iliac vein or of the vena cava, respectively, with due regard for control of the veins of both extremities. These

high proximal ligations, however, should be less frequently necessary if early ligation of the superficial femoral vein, preferably bilateral, in combination with other helpful measures, is performed. With this in mind, attention will be directed toward

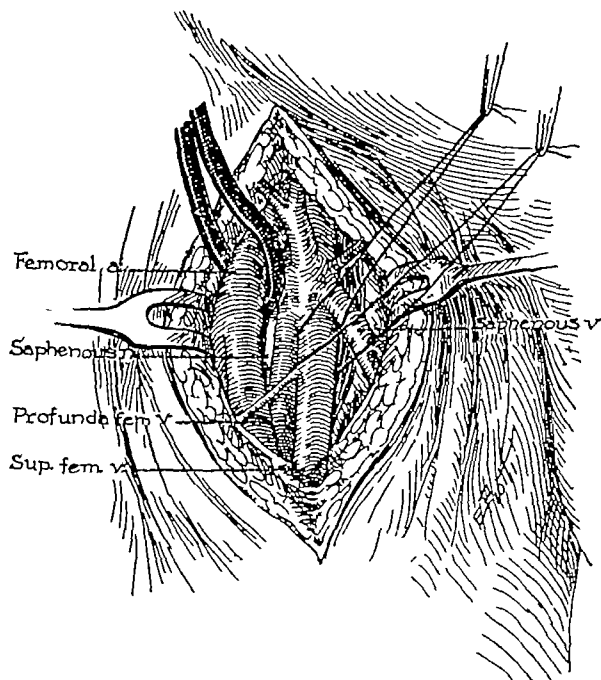


FIGURE 2 Isolation of the Superficial Femoral Vein. Exposure of the deep vessels is facilitated by preliminary retraction of the femoral artery. Care is taken to avoid injury to the great saphenous nerve. The profunda femoris vein is visualized.

the technical aspects of ligation of the superficial femoral veins.

Excellent results have been obtained with the use of local anesthesia for ligations below the inguinal ligament by the simple technic illustrated in Figure 1. After skin and subcutaneous infiltration with approximately 20 cc of 1 per cent novocain, 10 cc is injected through a needle inserted vertically to the level of the great vessels at a point overlying the fossa ovalis—that is, 2.5 cm lateral to and 1.5 cm below the anterosuperior spine. Careful aspiration guards against injection into a vessel. Usually, no further injection is required. This procedure has likewise proved eminently satisfactory for ligation of the saphenous vein and its tributaries.

An adequate, 8-cm longitudinal incision is made just medial to the pulsating femoral artery as a guide (Fig 2). Transverse incision may be extremely hazardous because of its restricted exposure at the level of the deep vessels and may interfere with the lymphatic drainage of the extremity. Generous exposure at the deep level is essential. The incision should not be allowed to become narrow and conical in depth, giving dangerously restricted exposure, especially when the perivascular inflammatory reaction is marked.

With retraction of the sartorius muscle laterally, care should be exercised against injury to the large saphenous nerve coursing in the fascia overlying Hunter's canal. This is the large terminal branch of the femoral nerve. Injury has not infrequently occurred, in my experience, producing disturbing hypesthesia along the inner lower thigh and leg areas.

There is nothing superficial about the superficial femoral vein. It lies not only medial to but also far below the femoral artery in Hunter's canal. It comes into view only when the femoral artery has been first exposed, carefully freed and retracted with soft rubber Penrose tubing. Because of the deep position of the vein the term "distal femoral" rather than

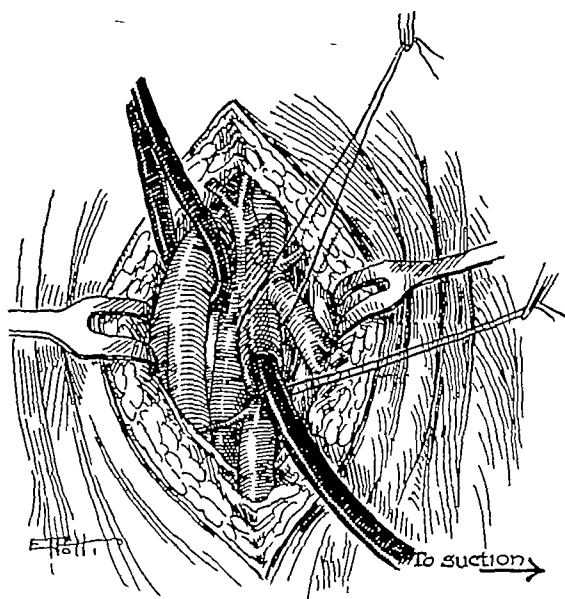


FIGURE 3 Removal of the Thrombus. Aspiration is continual until brisk retrograde flow is obtained. The distal vein segment is later aspirated.

"superficial femoral" vein has seemed more accurately descriptive.

Before a clamp is passed beneath the superficial femoral vein, the deep tributaries arising from the posterior aspect of the vein—namely, the profunda femoris and the large muscular branches—should be visualized. Failure to do this in one patient led to alarming deep hemorrhage, unrecognized damage to the femoral artery and mid thigh amputation for gangrene seven days later. In an additional patient with restricted operative exposure, the damaged portion of the femoral artery required resection, followed by anastomosis and immediate heparinization. This resulted fortunately in a successful outcome.

Isolation of the femoral vein just distal to the profunda femoris vein (Fig 3) prepares the vein for partial transection and gentle catheter or glass-tube aspiration of all proximal clot until brisk retrograde flow is obtained. It is my practice to

explore the profunda femoris vein with a hypodermic needle to aid in deciding whether to ligate proximal or distal to the profunda femoris vein. Additionally, ligation at the lower level is regarded as inadequate if there is proximal, adherent, fragmented thrombus that is removed with difficulty.

After brisk retrograde flow has been obtained and the proximal vein segment secured, aspiration of the distal vein segment is carried out before complete section and transfixion of the vein. It has been my impression that subsidence of the local thrombophlebitic reaction has thereby been encouraged.

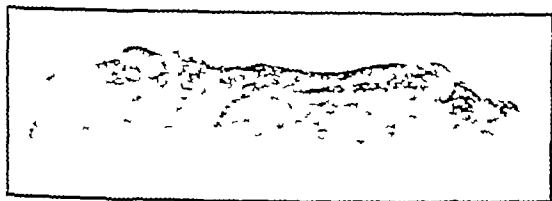


FIGURE 4 *An Organized Floating Thrombus*

Postoperatively, elastic bandages are applied from ankle to groin, and the patient is allowed out of bed as soon as his physical condition permits.

Figure 4 shows a nonadherent, organized thrombus 8 cm in length, removed from the right common femoral vein of a thirty-six-year-old infantry sergeant. The patient had sustained multiple battle wounds thirty-two days previously, including a compound fracture of the right tibia. Unexplained pain in the left side of the chest for thirty hours had been noted. X-ray films of the chest were unrevealing. There was slight tenderness over the femoral vein in the fractured leg. When the vein was opened there was brisk, apparently normal flow of blood as the midportion of the torpedo-shaped thrombus presented itself for easy removal. Recovery was uneventful.

Finally, in addition to vigorous prophylactic measures, it may prove wise in certain cases to ligate the superficial femoral veins bilaterally prior to a planned operation or long illness. Rigidly controlled indications for this should be well understood.

* * *

An ever-alert approach to the confined patient with emphasis on prophylaxis, early recognition and treatment with either anticoagulants or proximal ligation, or both, should offer the patient a large degree of protection against thromboembolism. It is toward the control of pulmonary embolism without warning, however, that preliminary ligation is largely directed.

In addition to early ligation distal to the profunda femoris vein, combined use of sympathetic blocks, heparin or dicoumarol and early rising should offer greater protection than ligation alone, not only

against thromboembolism but also against damage to the collateral vessels. Both vasospasm and obliterative endophlebitis spreading to the indispensable collateral vessels may thus be lessened. Judicious employment of a combination of helpful procedures, rather than any single procedure, may offer greater protection to the patient. Disturbing sequelae should be lessened, and the more drastic higher ligations less often necessary.

REFERENCES

1. Homans J. Diseases of veins. *New Eng J Med* 235 163-167 and 193 198 1946
2. Ochsner A. Intravenous clotting. *Surgery* 17 240 263 1945
3. Bauer G. Heparin therapy in acute deep venous thrombosis. *J A M A* 131 196-203 1946
4. Smithwick, R. H. Personal communication
5. Evans J. A. and Boller R. J. Subcutaneous use of heparin in anti-coagulation therapy. *J A M A* 131 879-882 1946
6. Allen, E. V. Challenge of thrombosis and embolism of blood vessels and clinical use of anticoagulants. *Quart Bull., Northwestern Univ. M School* 20 1-7 1946

DISCUSSION

Dr. JOHN HOMANS (Boston). Dr. Albright has covered a good deal of ground with a great deal of intelligence and common sense. It is rather difficult to find fault with anything he has said about thrombophlebitis. I am perfectly certain that he has a comprehensive understanding of it.

It seems to me that if I were to criticize, in a friendly way, his presentation, I should say that he had drawn a good many conclusions from his military experience, if I understand him correctly, in the surgery of these youngish patients. I have previously heard discussion of the matter of thrombosis in such patients, and apparently when the man of military age suffers a thrombosis he tends to become extremely thrombophilic, the ordinary methods of handling this thrombosing process seem to work in different ways from those of older persons. I have heard of a good many vena-cava ligations and so forth.

Actually, I find myself more interested in these days in the problem of thrombosis in cardiac and medical patients who really offer a continuing problem, because they are confined to bed with serious disease and the matter of preventing them from having thrombosis and embolism is quite a different one from what it would be in younger persons — for instance, those who have suffered accidents or have been operated on.

I suppose one must decide, as I am sure the Massachusetts General Hospital group have decided, that there are certain cases that can be handled in no other way than by prophylactic vein division — for example, patients who must be operated on for serious abdominal diseases. Such patients, and probably some of the cardiac patients as well, can evidently be subjected to a superficial femoral division with a great deal of satisfaction.

The Swedes have an interesting idea of trying to prevent thrombosis from rising above the knee — above the popliteal vein — on the ground that once the thrombosis reaches the femoral vein, that vein will be crippled and the future of the leg will present quite a serious problem. They have therefore decided to try to make an early diagnosis under the usual circumstances in which thrombosis is likely to arise. Then they attempt to prevent the progress of the process by the use of anticoagulants. In a way, that is a more reasonable approach to the subject than the use of the division of the vein. And I must say that I am sympathetic with it.

I should like to go a little farther and say that in the occasional patient who suffers a thrombosis below the knee in everyday life the future is likely to be a great deal brighter if the process can be subdued by anticoagulants than if the femoral vein is divided. The question is whether there is an equal amount of safety in the two procedures. I am still utterly uncertain about that point, but having divided a good many veins in persons with fairly extensive thrombosis that has probably not already crippled the superficial femoral vein, I should rather not divide a femoral vein if I can stop the process from rising to the level of the groin by the use of anticoagulants. That is a point of view that Dr. Albright

did not present. I should like to hear his opinion about it.

His system of operating on patients who already have a fairly extensive process, I think, is ideal. I do not like divisions of the common femoral vein above the profunda. If it is safe to remove the thrombus by opening of the femoral vein below the profunda and especially if afterward one can make use of anticoagulants, that seems a better way to handle the process.

I should like to have Dr Albright's view on the use of anticoagulants after division of the superficial femoral vein. I know that there are a great many other aspects of this subject. I have merely spoken of some that occurred to me as being among those that perhaps Dr Albright did not go into with great detail.

DR ARTHUR W ALLEN (Boston) I am amazed at how closely Dr Albright's paper follows my own views on the treatment of thrombophlebitis, and I should like to congratulate him on having presented it as well and as quickly as he did. In other words, I agree with him that we have three useful measures of treatment at our disposal, and quite often all three should be used.

I want to speak for a moment about the prophylaxis of thrombosis. I am quite sure that the future primarily holds for us the duty of preventing the patient from developing a thrombosis with a possible embolism. Patients in the young and middle age groups who do not have diseases that contraindicate the use of anticoagulants can safely be protected from thrombosis by a controlled, careful use of heparin and dicoumarol, but there is a limit to the number and the type of cases to which this can be applied.

The high incidence of thrombosis and embolism in older patients, particularly those with leg injuries, as Bauer, Veal and Homans have emphasized, is to be considered in a slightly different category.

In the treatment of thrombosis to prevent further embolism, we soon learned that we should interrupt both femoral veins. We were much interested to find that if we interrupted a normal femoral vein, symptoms such as swelling in the legs rarely occurred. This came as quite a surprise in spite of the fact that the femoral vein had formerly been interrupted in an effort to benefit the circulation in cases of thromboangitis obliterans. A short period of edema that did not always occur was expected, but I think that the significance of this did not register until we had experience with a great many hundred cases, in which it was found that if the vein was interrupted before thrombosis developed, the sequelae were negligible.

In 50 consecutive cases of fractures about the hip we have recently interrupted prophylactically the superficial femoral vein bilaterally. In none of those patients has an embolism occurred, and in none has any evidence of thrombosis appeared.

In the preceding 50 cases, which were exactly identical and did not have this prophylactic interruption, there were 5 proved fatal cases of pulmonary embolism, — a rate of 10 per cent, — and there were 2 additional patients who died similarly, probably from embolism, although no autopsy was performed.

We have now more than 450 patients in the older age group who would formerly have been treated in bed for one cause or another but who have had what we consider prophylactic femoral-vein interruption. In other words, interruption has been done shortly after the period of bed rest has been necessary and theoretically before any thrombosis has occurred. There has been only 1 case in which a fatal embolism later occurred. In that group we should have expected a great many deaths from embolism. There has only been 1 case of a mild thrombophlebitis below the knee, as well as a few cases of minor transient edema, but most of the patients showed no signs or symptoms from this adequate protection against thrombosis and embolism.

DR E EVERETT O'NEIL (Boston) Perhaps my opinion and my position are somewhat unfair, but some years ago when we first started using heparin and dicoumarol, we had an extremely unfavorable experience with the anticoagulants. For that reason we soon forsook our position in using them as a form of therapy and have subsequently adhered rigidly to the division of large veins as a measure of handling deep venous thrombosis.

Like Dr Homans we have in most cases practiced division of the superficial femoral vein, and for similar reasons. Our

experience with division of the deep femoral veins has not been good, because we have found that there have been many cases in which residual swelling has persisted for long periods, beyond what we have seen in division of the superficial femoral veins.

That is perhaps an academic matter, however. Nevertheless, the operation of dividing the superficial vein is slightly easier than dividing the common femoral, and perhaps lends itself more easily to practice by residents and house officers, who usually do the operation in the large hospitals.

So far as the anticoagulants are concerned, surgeons are interested in using some procedure that may guarantee before operation that venous thrombosis will not occur. Anticoagulants certainly cannot be used before operation, and there therefore is no guarantee that the patient will not die of embolism one or two days or even hours following the operation, because what has not been stressed by the proponents of anticoagulants is that thrombosis may be present long before operation has been started and, as I have suggested, lethal embolism may occur shortly thereafter. Therefore one must take the quickest measure of circumventing this catastrophe, and that, in my opinion, is division of the proper veins.

Our opinion of prophylactic venous divisions is similar to that of Dr Allen. More and more prophylactic venous divisions will be done in properly selected groups, which we know by experience lend themselves to venous thrombosis.

I think — and this fact should be emphasized — that when a normal femoral vein has been divided, swelling seldom if ever occurs, and that brings up the point that early diagnosis in deep femoral thrombosis is the *sine qua non* of success in the handling of these cases.

If the diagnosis is made early and the veins are tied early, not only will more lives be saved but also many of these complications, such as swelling, will be averted.

DR DONALD MUNRO (Boston) As a result of my experience and from listening to the paper and the discussions, I am confused regarding certain aspects of this problem. I gather from what has been said that it is considered important that patients be mobilized early — particularly the legs — to prevent the development of thrombosis and embolism and that in pursuance of that ideal, prophylactic ligation of the femoral veins has met with widespread approval.

I do not understand why patients that I see who have been paralyzed as a result of spinal-cord injuries, whose legs are certainly as immobile as possible and who lie in bed for months or often for years do not get femoral thrombosis or embolism even though the veins have not been ligated prophylactically or therapeutically.

I have rather detailed knowledge of about 250 such cases. Although I cannot give the exact figures, I do not believe that we have had any patient who died as a result of pulmonary embolism among this group, and I am sure that the incidence of femoral thrombosis is so low as to be negligible.

I have also less intimate knowledge of between 500 and 600 similar patients that I have seen in various Army hospitals. Two hundred of them I am quite familiar with. Certainly, femoral thrombosis and pulmonary embolism in those cases were so rare that in no hospital that I have visited has the question been raised whether there was any need to do anything to prevent such complications.

DR ALBRIGHT (closing) Regarding the use of anticoagulants to prevent progression of the clot from the leg to the femoral vein, it is difficult to pass judgment. Heparin in Pitkin menstruum may be employed, and I prefer that to dicoumarol. From recent experience, Dr E V Allen has stated that small doses of dicoumarol that reduce the prothrombin time slightly will not affect the coagulation time or the clot. There must be a reduction of the prothrombin time to 30 per cent or less. If it is between 30 and 100 per cent, no effect has been produced by the dicoumarol.

I have no objection, if one decides to use anticoagulants, to using them well and effectively. Pitkin solution of heparin can be given easily, in small subcutaneous doses, the effect lasting for two days, and controlled by venous clotting times. Dicoumarol requires two or three days to become effective, and if one wishes to stop it, its effect lasts an additional few days.

The anticoagulant may be started usually two days after ligation. Intravenous heparin clears from the blood within a few hours, and may be stopped if a bleeding tendency occurs.

In vascular surgery, especially in arterial anastomosis, heparin has frequently been used without untoward effect. In my experience bleeding occurred more frequently in large avulsed wounds, controlled by discontinuance of the heparin and pressure dressing.

I am quite conscious of the fact that these Army patients were young. My civilian patients have been largely in the group over forty years of age.

In patients with fractures as Dr. Allen pointed out, I believe that prophylactic ligation should be given proper consideration. Overseas, the wards were filled with patients in casts. It was extremely difficult to evaluate leg pain, fever and the question of venous tenderness by palpation under the edge of the cast at the groin or midhigh level. The decision whether the pain was caused by the regional swelling about the fracture, infection or thrombophlebitis proved a real problem. Consequently, several patients had chest signs before ligation was carried out.

Dr. O'Neil has emphasized the desirability and urgency of early ligation, with which most of us agree. Actually a certain number of patients are first seen in an advanced, late stage of thrombophlebitis requiring ligation at higher levels. This makes it difficult to lessen the incidence of postoperative disturbances, which tend to limit the acceptance of this procedure.

Dr. Munro wishes to know why his paralyzed patients do not get thrombosis or embolism. Because of the paralysis from the waist down, there is no factor of vasospasm or arteriolar spasm. Ochsner considers the element of vasospasm so important that he teaches his medical students to perform repeated lumbar sympathetic blocks with novocain, regardless of whether ligation is performed or heparin given. The absence of vasospasm in these young patients, who have excellent cardiovascular systems with efficient muscle and elastic vessel walls probably constitutes the chief explanation of the infrequent thrombi.

THE EFFECT OF RESTRICTED INTAKE OF CAROTENE AND VITAMIN A ON PSORIASIS VULGARIS*

A Preliminary Report

RICHARD HOFFMANN, M.D. † EVELYN J. LORENZEN, Ph.D., ‡ AND ARLENE S. GARFINKEL, B.A.

BOSTON

KNOWLEDGE concerning the etiology and pathophysiology of psoriasis vulgaris is limited. Certain characteristics of the disease are generally recognized, however. One of the main physiologic functions of the epidermis is the production of keratin necessary for the protection against and for the repair of injuries to the cutaneous system. In the skin of a psoriatic person the mechanism of keratinization fails whenever increased demands on the protective and reparative processes of the epidermis occur. Instead of completely keratinized cells, defectively cornified—that is, parakeratotic cells—are produced.¹⁻³ The extent and degree of the parakeratosis are related to the clinical activity of the psoriasis. In early stages the characteristic parakeratosis usually extends uniformly across the lesion, becoming even more uniform and greater in rapidly developing and progressing lesions. Quiescent and healing lesions show hyperkeratosis in place of or together with parakeratosis.⁴⁻⁶ Psoriasis rarely occurs in Negroes.⁷⁻¹⁰ This may be explained by the greater thickness of the stratum corneum of the skin in Negroes as compared with that of the skin in Whites,⁹ and by its greater resistance to external irritants.⁹⁻¹¹ Both properties oppose the establishment of psoriasis. Careful sun treatment, local application of tar, sulfur, chrysarobin and so forth and internal administration of inorganic arsenic compounds are widely recognized as beneficial agents in the treatment of psoriasis. Various factors are operative in the action of these remedies. They have in common, however, a distinct keratoplastic effect, which may be of importance in the correction of the defective keratinization.

A low-fat diet has likewise received favorable recognition in the treatment of psoriasis. Grütz

TABLE 1 Dietary Allowance of Foods Containing Vitamin A^{12, 13}

Foods†	Amount	Vitamin A Content international units
Breads and cereals		
Baking-powder biscuit, medium size	1	25
Wheat germ	1 tablespoon	40
Dairy products		
Buttermilk	1 glass	50
Skimmed milk*	1 glass	50
Cottage cheese	1 tablespoon	20
Fruits		
Applesauce, canned	1 sauce dish	50
Blackberries, canned	1/2 cup	20
Cherries, white, canned	12	10
Cranberry sauce	5 tablespoons	10
Dates	4	50
Figs, dried	1/2	20
Grapefruit, medium size	1/2	20
Grapefruit juice	1/2 cup	10
Grapes, green	20	20
Honeydew melon	1 1/2	10
Peas*, medium size	1	30
Raisins	1 1/2 cup	30
Strawberries	10	50
Vegetables		
Beet, medium size	1	0
Cabbage, white	1/2 cup	20
Cauliflower	1/2 cup	20
Celery hearts	3 stalks	15
Cucumber, peeled	8 slices	15
Eggplant	1/4 cup	20
Lentils, cooked	1/2 cup	15
Onions, mature, medium size	2	30
Potato, white, medium size	1	40
Radishes	10	10
Sauerkraut	2 1/2 cup	15
Turnip, white	1/2 cup	15
Meats		
Bologna	4 slices	10
Frankfurt, medium size	1	25
Fish		
Cod	4 oz.	10
Haddock	4 oz.	10
Halibut	4 oz.	15
Trout	3 oz.	10
Whitefish	3 oz.	10
Desserts		
Walnuts	5	20

*Patients were instructed to select foods from each group the daily total being within the individual allowance of vitamin A.

*Patients were instructed to consume 2 glasses of skimmed milk daily or supplementary calcium (calcium dihydrophosphate) was prescribed.

and Bürger,¹² the originators of this therapy, concluded that psoriasis was a "lipodosis" and that a

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†This study was supported in part by a grant from the Leanne Maise Company Fund to Harvard Medical School.
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lowering of the fat content of the cutaneous elements was the basis of the beneficial effect. There has been considerable disagreement, however, regarding both the theoretical basis for this treatment and the findings of increased lipids in the serum and in the skin of psoriatic patients^{4, 8, 12-17}

Since a defect in the reactive process of keratinization appears to be an essential factor in the pathophysiology of psoriasis and since keratoplasia is observed in vitamin A deficiency,¹⁸⁻²⁰ it occurred to us that the improvement of psoriasis subsequent to the Grütz-Burger low-fat diet might be due

ated every two weeks by the dietitians of the Food Clinic. To ensure an adequate intake of other essential nutrients, supplements of vitamin B complex, ascorbic acid and iron were added to the diet in the majority of cases. Patients were specifically instructed to consume a sufficient amount of fats free of vitamin A to compensate for the omission of fats containing vitamin A. No local treatment except white vaseline was used.

Physical examinations were repeated at intervals of two to four weeks. Skin biopsies were examined microscopically in the majority of patients before

TABLE 2 *Effect of Diet Restricted in Carotene and Vitamin A*

CASE No	SEX	AGE	DURATION OF PSORIASIS	TYPE OF LESIONS	DURATION OF DIET	INTERVAL BEFORE SLIGHT IMPROVEMENT	INTERVAL BEFORE MARKED IMPROVEMENT	INTERVAL BEFORE COMPLETE CLEARING
1	F	yr 65	yr 55	Generalized nummular and discoid erythrodermatic, spreading	mo 7	wk —	wk 8	wk 16
2	F	36	Since childhood	Generalized nummular and discoid erythrodermatic, spreading	12	8	14	40
3	F	22	5	Generalized erythrodermatic	8	5	10	14
4	M	53	8	Generalized nummular discoid	9 5	10 —	18 16	— —
5	M	43	2	Discoid	11	—	8	20
					5	8	16	—
6	M	34	10	Nummular discoid	4 1	10 4	— —	16 —
7	M	49	12	Inveterate discoid	7	—	—	—
8	F	37	17	Generalized discoid and nummular	8	10	—	14
9	F	40	3	Generalized erythrodermatic and discoid	6	12	16	—
10	M	25	Since childhood	Generalized discoid	3½	12	—	—
11	F	31	Since childhood	Guttate nummular discoid	5	—	14	20

to the simultaneous decrease in the supply of vitamin A. The purpose of this investigation is to observe the influence of a diet low in vitamin A on the clinical course of psoriasis.

PROCEDURE

Only patients who had had extensive psoriasis vulgaris of long duration without experiencing spontaneous remissions were studied. A maximal daily intake of 150 to 300 international units of vitamin A was allowed (Table 1). Foods containing more than 50 international units of vitamin A per average serving were prohibited whereas foods free of vitamin A were allowed in unlimited amounts. A record of the daily intake of each patient was evalu-

ated every two weeks by the dietitians of the Food Clinic. To ensure an adequate intake of other essential nutrients, supplements of vitamin B complex, ascorbic acid and iron were added to the diet in the majority of cases. Patients were specifically instructed to consume a sufficient amount of fats free of vitamin A to compensate for the omission of fats containing vitamin A. No local treatment except white vaseline was used.

Physical examinations were repeated at intervals of two to four weeks. Skin biopsies were examined microscopically in the majority of patients before the diet was begun and thereafter at intervals of three to six months.

Clinical supervision and the reports of the patients regarding adherence to the diet had to be relied on in the early stage of the investigation. At present, in conjunction with the clinical observations, the plasma carotene and vitamin A levels are determined periodically by the colorimetric method of Kimble.³² These data afford an objective measure of the patient's co-operation in adhering to the diet, an insight into the extent of the correlation between the clinical and biochemical changes and some assurance that a harmful degree of vitamin A deficiency has not developed.

OBSERVATIONS

In 9 of 11 cases the psoriatic lesions markedly improved or completely cleared within eight to forty weeks after the initiation of the diet restricted in both carotene and vitamin A (Table 2). The first definite signs of improvement appeared within four and twelve weeks. Since spontaneous amelioration is frequently experienced during the summer months,²⁴ improvement noted during the months of April to October was not considered significant.

within eight weeks after the initiation of a dietary regime restricted to 800 international units of vitamin A. No untoward effects were observed in any other patient.

In 6 patients who had shown marked improvement or complete clearing of the lesions, relapses occurred within three to eight weeks consequent to the resumption of a normal unlimited diet, and in 1 patient six weeks after supplementation of the restricted diet with carotene. Within two weeks after the carotene supplementation had been dis-

TABLE 2 (Continued)

CASE No	PLASMA CAROTENE CONTENT		PLASMA VITAMIN A CONTENT		RELAPSE
	RESTRICTED DIET	NORMAL DIET	RESTRICTED DIET	NORMAL DIET	
	microgm/100 cc	microgm/100 cc	microgm/100 cc	microgm/100 cc	
1	—	—	—	—	On daily vitamin A intake of 1500 international units only few nummular lesions on elbows and forearms after 8 wk. resumption of normal diet followed in 8 wk. by relapse; slight spreading during following year; no change in weight on diet.
2	—	11½	—	38	After 16 wk. on daily vitamin A intake of 2000 international units 1 nummular lesion on each hip, which became slightly larger in next few months; no generalized spreading during last 2 winters; weight varied from 110 to 115 pounds.
3	—	—	—	—	Weight gain from 10½ to 118 pounds on restricted diet; resumption of normal diet followed in 8 wk. by relapse.
4	—	—	—	—	No change in weight on diet; no further improvement observed on daily vitamin A intake of 1500 international units for 5 mo.
5	60 61	—	47 48	—	Slight relapse after 11 mo. on restricted diet, followed by continued spreading; diet discontinued on complaint of fatigue, anorexia and weight loss of 6 pounds.
	64 80 90	—	34 38 38	—	Daily intake of approximately 800 international units of vitamin A in 2nd phase.
6	—	—	—	—	Relapse 4 wk. after resumption of normal diet followed by continued spreading; another relapse with continued spreading 8 wk. after resumption of normal diet.
7	—	—	—	—	No improvement; patient unable to maintain normal caloric intake on restricted diet; weight loss of 9 pounds.
8	48 55 37	75 51	35 56 42	35 40	Weight gain of 7 pounds on restricted diet; relapse 6 wk. after supplementation of intake with carotene equivalent to 20,000 international units of vitamin A daily.
9	18 38	41	28 30	23	Relapse 6 wk. after change to diet restricted only in vitamin A intake; weight loss from 112 to 105.5 pounds.
10	<7 14	22 63	44 43	44 55	Relapse 3 wk. after resumption of normal diet because patient was unable to maintain a normal caloric intake and lost 5 pounds in weight.
11	21	—	48	—	No weight change on diet.

*Carotene intake unlimited. 3 tablespoons of mineral oil daily added to diet, since mineral oil has been shown to interfere partially with absorption of carotene from the gastrointestinal tract.²⁵

Of the 6 female patients 5 showed complete clearing, and 1 marked improvement, whereas of the 5 male patients 2 showed complete clearing, 1 marked improvement and 1 slight improvement and 1 remained unimproved. One patient (Case 5), whose lesions had completely subsided within twenty weeks, experienced a slight relapse after having been on the restricted diet for eleven months. He was unable to maintain a sufficient caloric intake, had lost 6 pounds and complained of tiredness and anorexia. These symptoms disappeared soon after the resumption of a normal unlimited diet, the psoriasis, however, continued to spread during the following ten months. Improvement was observed

continued this patient again showed marked improvement.

Plasma carotene and vitamin A determinations were not done in these cases prior to the beginning of the diets low in vitamin A. Determinations in 6 patients during the dietary regime, however, ranged from an undeterminable amount to 80 microgm of carotene and from 23 to 48 microgm of vitamin A per 100 cc of plasma. For comparison, the plasma values of 26 normal subjects on an unrestricted dietary regime showed an average of 149 microgm of carotene (range, 65 to 237 microgm) and an average of 43 microgm of vitamin A (range, 26 to 64 microgm) per 100 cc.

Corresponding values in 25 other psoriatic patients prior to dietary treatment were 139 microgm of carotene (range, 65 to 310 microgm) and 51 microgm of vitamin A (range, 28 to 73 microgm) per 100 cc of plasma. To date, plasma carotene and vitamin A levels have been determined at intervals of two weeks in 8 of these patients who have been on the restricted diet for a period up to ten weeks. The carotene levels showed a reduction of from 35 to 68 per cent of the original value within the first two or three weeks and continued to decrease, whereas plasma vitamin A values remained unchanged.

DISCUSSION

Wald et al.³⁵ showed that subjects saturated with vitamin A did not develop signs of vitamin A deficiency even after a period of about six months on a diet limited to 100 international units or less daily. Within slightly more than a week after the deficient diet had been begun, the plasma carotenoids dropped from normal to extremely low levels. The plasma vitamin A levels, however, maintained the initial maximal values throughout the entire deficiency. Our findings are in accordance with the results of these authors and similar observations reported by Brenner and Roberts.³⁶

The lack of noticeable changes in vitamin A plasma levels coincident with vitamin A restriction, however, does not exclude the possibility of a reduction of the vitamin in body stores that might be biologically effectual prior to a measurable decrease in plasma vitamin A levels. Lindqvist³⁷ observes that functional changes that are undetectable by available methods may occur before a decrease of the plasma vitamin A levels and other typical deficiency symptoms become apparent.

Furthermore, the possibility that the carotene itself had a direct influence on skin metabolism must be considered. It has been pointed out that the conversion of carotene to vitamin A probably occurs in other tissues besides the liver^{38, 39} and that the carotene may have biologic functions in addition to being the precursor and main source of vitamin A.³⁹⁻⁴¹

It should again be emphasized that the restricted diet used in this study included a normal amount of fat. This eliminates the possibility that a decrease of the cellular fat content of the epidermis thought to be achieved by the Grütz-Bürger low-fat diet is the specific mechanism responsible for the favorable reaction of psoriasis to the low vitamin A diet.

No definite statement, however, can be made regarding whether or not stimulation of keratinization due to vitamin A restriction is the basis for the observed improvement. Further investigation of these problems is necessary.

SUMMARY

Eleven patients with severe and persistent psoriasis vulgaris were maintained on a restricted diet

allowing 150 to 300 international units of vitamin A daily. Seven patients showed complete clearing of the lesions, 2 marked improvement, 1 slight improvement and 1 no improvement. Relapses occurred in 7 previously improved patients consequent to the resumption of a normal unrestricted diet or supplementation of the restricted diet with carotene.

The values of the plasma carotene and vitamin A levels determined in 6 cases while the patients were on the restricted diet are compared with those of 26 normal persons and 25 psoriatic patients on an unrestricted dietary regime.

The theoretical basis of this study and the related problems of carotene and vitamin A metabolism are discussed.

This dietary restriction is not considered a practical therapeutic regime. It affords an opportunity for further investigation of the metabolic aspects of psoriasis.

REFERENCES

1. Samberger, F. Über das Wesen der Psoriasis. *Acta dermat venereol* 2: 359-369, 1921.
2. Brocq, L. Quelques réflexions sur l'étiologie du psoriasis à propos des récentes publications américaines. *Ann de dermat et syph* 5: 156-183, 1910. Étude clinique du psoriasis au moyen du grattage méthodique. *Ibid* 6: 221-232, 1916-17.
3. Unna, P. G. *The Histopathology of the Diseases of the Skin*. Translated by N. Walker. 1233 pp. New York: MacMillan Co. 1896. Neuere Erfahrungen und Anschauungen über Psoriasis. *Med Klin* 2: 1011-1015 and 1037-1041, 1906.
4. Burks, J. W., and Montgomery, H. Histopathologic study of psoriasis. *Arch Dermat & Syph* 48: 479-493, 1943.
5. Haslund, P. Die Histologie und Pathogenese der Psoriasis. *Arch f Dermat u Syph* 114: 427-492 and 745-814, 1912.
6. Gans, O. Psoriasis. In *Histologie der Hautkrankheiten*. Vol. 1. Normale Anatomie und Entwicklungsgeschichte. 656 pp. Berlin: Julius Springer, 1925.
7. Lewis, J. H. *The Biology of the Negro*. 433 pp. Chicago: University of Chicago Press, 1942.
8. Hazen, H. H. Skin diseases in American negro. Personal observations upon skin diseases in American negro. *J Cutan Dis* 32: 705-712, 1914.
9. Fox, H. Observations on skin diseases in negro. *J Cutan Dis* 26: 67-79 and 109-121, 1908.
10. Schamberg, J. F. Known and unknown about psoriasis. *J A M A* 83: 1211-1214, 1924.
11. Schwartz, L., and Tulipan, L. *A Text Book of Occupational Diseases of the Skin*. 799 pp. Philadelphia: Lea & Febiger, 1939.
12. Grütz, O., and Bürger, M. Die Psoriasis als Stoffwechselproblem. *Klin Wchnschr* 12: 373-379, 1933.
13. LeWinn, E. B., and Zugerman, I. Fat tolerance tests in psoriasis. *Am J M Sc* 201: 703-711, 1941.
14. MacKee, G. M., and Foster, P. D. Histopathogenesis of psoriasis and its aberrant lesions. *Arch Dermat & Syph* 34: 35-56, 1936.
15. Madden, J. F. Cholesterol balance and low fat diet in psoriasis. *Arch Dermat & Syph* 39: 268-277, 1939.
16. Schaaf, F., and Obulowicz, M. Lipidstoffwechsel und Psoriasis. (Quantitative Bestimmung der einzelnen Lipidfractionen bei Psoriasis und Nicht-Psoriasis im Nüchternserum und nach Fettbelastung.) *Arch f Dermat u Syph* 173: 200-211, 1935.
17. Schreiner, K., and Bilger, W. Lipidstoffwechseluntersuchungen bei der Psoriasis. *Dermat Wchnschr* 94: 505-511, 1932.
18. Frazier, C. N., and Hu, C. K. Nature and distribution according to age of cutaneous manifestations of vitamin A deficiency: study of 207 cases. *Arch Dermat & Syph* 3: 825-852, 1936.
19. Frazier, C. N., Hu, C. K., and Chu, F. T. Variations in cutaneous manifestations of vitamin A deficiency from infancy to puberty. *Arch Dermat & Syph* 48: 1-14, 1943.
20. Lehman, E., and Rapaport, H. G. Cutaneous manifestations of vitamin A deficiency in children. *J A M A* 114: 386-393, 1940.
21. Loewenthal, L. J. A. New cutaneous manifestation in syndrome of vitamin A deficiency. *Arch Dermat & Syph* 28: 700-708, 1933.
22. Moul, F. H. Histopathology of rat skin in avitaminosis A. *Arch Dermat & Syph* 47: 768-777, 1943.
23. Reiss, F. Contribution to cutaneous manifestations of vitamin A deficiency. *Chinese M J* 50: 945-948, 1936.
24. Sweet, L. K., and Kang, H. J. Clinical and anatomic study of avitaminosis A among Chinese. *Am J Dis Child* 50: 699-734, 1935.
25. Wolbach, S. B. Pathologic changes resulting from vitamin deficiency. *J A M A* 108: 7-13, 1937.
26. Wolbach, S. B., and Bessey, O. A. Tissue changes in vitamin deficiencies. *Physiol Rev* 22: 233-289, 1942.

- 7 Weitsch S B. and Howe P R. Tissue changes following deprivation of fat soluble A vitamin *J Exper Med* 42 753-777 1925
- 8 *Idem*. Vitamin A deficiency in guinea-pig *Arch Path & Lab Med* 5:230-253 1928
- 9 Loumans J B., and Corlette M B. Specific dermatoses due to vitamin A deficiency *Am J M Sc* 195 644-650 1938
- 10 Bowers A deP. and Church, C F. *Food Values of Portions Commonly Used*. Fifth edition 46 pp Philadelphia Philadelphia Child Health Society 1944
- 11 Bureau of Human Nutrition and Home Economics U S Department of Agriculture In co-operation with National Research Council *Tellus of Food Composition in Terms of 11 Nutrients* Miscellaneous Publication 572 70 pp Washington, D C Government Printing Office 1945
- 12 Kimble M S. Photocolorimetric determination of vitamin A and carotene in human plasma *J Lab & Clin Med* 24 1055-1065 1939
- 13 Alexander B. Lorenzen E J. Hoffmann R. and Garfinkel A. Unpublished data
- 14 Lane C G. and Crawford G M. Psoriasis: statistical study of two hundred and thirty-one cases *Arch Dermat & Syph* 35 1051-1061, 1941
- 15 Wad G. Brouha L. and Johnson R E. Experimental human vitamin A deficiency and ability to perform muscular exercise *Am J Physiol* 137 531-556 1942
- 16 Brenner S. and Roberts L I. Effects of vitamin A depletion in young adults *Arch Int Med* 71 474-482 1943
- 17 Lindqvist J T. *Studier över det Vitamin A-brist Mänsker* Upsala Appelbergs Boktryckeriskuebolag 1939 P 52
- 18 von Euler H. Die biochemischen und physiologischen Wirkungen von Carotin und Vitamin A *Ergeb d Physiol* 34:360-405, 1932
- 19 Morton R A. *The Application of Absorption Spectra to the Study of Iodine, Hemocyanin and Coenzymes* Second edition 226 pp London Adam Hilger Ltd 1942
- 20 Zechmeister L. *Carotenoids* 338 pp Berlin Julius Springer 1934
- 21 *Idem*. Die Carouinoide im menschlichen Stoffwechsel *Ergeb d Physiol* 39 117-191 1947

TIME OF ELECTION FOR ABDOMINAL SURGERY IN CHILDHOOD*

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THE majority of abdominal surgical conditions in children under one year of age are due directly to some developmental anomaly. Infection, which plays a minor role in the abdominal surgery of the first year of life, subsequently forms the basis of many pathologic processes as it does in adult life. The processes found in infants are identical with those observed in adults, except that they are modified by conditions peculiar to early life. The modifying factors are often not entirely a disadvantage to the surgeon, for an infant's failure to co-operate makes the examiner observe more carefully and judge more keenly.

The process of growth and development has a definite effect on the course of many diseases in infancy and childhood. These factors frequently make disease sudden in its onset, short in its course and more intense in its manifestations. These same processes, however, often come to the aid of the surgeon, as they do in overcoming by growth the malalignment of a fracture or in the spontaneous healing of an incisional hernia.

It has been stated, and I believe quite without justification, that diagnoses are much more difficult to make in children than in adults. It is true that the surgeon must make his diagnosis not only without the co-operation of the child but also, at times, in spite of the child's efforts. I believe that if the examiner follows a definite pattern in his examination, seizing his opportunities as they present themselves and first of all gaining the child's confidence by not hurting him, the effort will be highly successful.

Anyone who considers an infant as a small edition of an adult will encounter many difficulties. Children tolerate the loss of fluid, particularly blood,

much worse than adults do. Gentle handling of the tissues, with careful hemostasis, is one of the first rules of abdominal surgery in childhood. Infants resist vigorously up to a certain point, but it should not be forgotten that there is a definite limit to the amount of surgery that a baby can tolerate. There is practically no indication for the exploratory laparotomy performed in adults, nor is there any abdominal condition so acute that the child need be operated on before he is properly hydrated. Many an excellent operation has been spoiled because the baby was dehydrated, anemic, exhausted and in no condition to stand the operation when it was performed, whereas a delay of perhaps an hour or two would have made success unquestionable.

This paper deals with the time of election for abdominal surgery of children. That there is a time of election for many operations goes without saying. The scope of such a title, however, makes it necessary for me to group many of the more frequent conditions since time does not permit a more detailed description of many of them.

The earliest emergency, which requires attention when the baby is but a few hours old, is hernia into the umbilical cord. The sac of the hernia, made up of amnion and peritoneum, is so thin, that, when it gets dry, it cracks and thereby permits infection to enter the peritoneal cavity from the outside. Many of these infants are operated on when they are less than twelve hours old. The umbilical vessels are ligated within the peritoneal cavity, the sac cut away, and the defect in the abdominal wall closed with through-and-through silk sutures.

A much more serious condition, making itself evident when the baby receives his first drink of fluids, is congenital atresia of the esophagus. In 85 per cent of cases the anomaly consists of an upper, closed esophageal pouch, completely separated from the lower pouch, that communicates with the trachea at or near the bifurcation. In the

*Presented at the New England Postgraduate Assembly Boston October 30 1946

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presence of great distress when the baby is first fed, atresia of the esophagus should be suspected, the suspicion is confirmed if the passage of a catheter encounters a complete obstruction 12 to 15 cm from the anterior alveolar margin. Such infants should have an immediate operation. If the diagnosis is not made before the age of three or four days, aspiration pneumonia will have occurred when the surgeon is ready to operate, owing to the aspiration of secretions from the upper esophageal pouch. Although an exploration may be done with local anesthesia, every hour that is saved in making the diagnosis improves the chances of survival. The ideal operation is end-to-end anastomosis of the two esophageal segments. Unfortunately, this is not always possible to accomplish because of the shortness of the upper esophageal pouch. Anastomosis, if done with the slightest pressure on the suture line, almost always fails.

Pyloric stenosis occurs about seven times more frequently in boys than in girls and often in the first child of the family. The Fredet-Ramstedt operation is curative and should be done just as soon as the diagnosis has been made by palpation of the tumor and as soon as the baby is completely hydrated. The tumor must be felt in every case of pyloric stenosis. If such a criterion is not established, many infants are needlessly operated on for pyloric stenosis.

Congenital obstructions of the duodenum may be divided into two main groups, depending on whether the obstructive lesion is in the lumen of the duodenum (intrinsic) or due to some extraluminal condition (extrinsic). The extrinsic lesions are duodenal bands, volvulus and fixation of the duodenum in an abnormal position. These lesions usually start as incomplete obstructions and become complete perhaps while the baby is in the hospital for observation. The intrinsic lesions comprise diaphragm or membrane, atresia of the duodenum and stenosis of the lumen, and usually give symptoms of complete obstruction immediately after birth, requiring an extensive abdominal operation when the infant is but a few hours old. Success with this type of surgery depends on how quickly the diagnosis is made and on the thoroughness of preparation before operation.

The diagnosis of intestinal obstruction in the newborn may be made by the taking of a flat plate of the abdomen. The site of obstruction is often determined in this way from the configuration and distribution of gas shadows, but it is rarely possible to state exactly what the cause of obstruction is. Any patient with intestinal obstruction should be operated on without delay, for an hour or two frequently makes considerable difference in the success of the operation. I should like to emphasize the use of the plain film rather than to delay operation to take x-ray films using barium or some other medium. All the information necessary may be

obtained by a plain film. Mixtures, such as barium, are dangerous in a potential intestinal obstruction, since an incomplete obstruction may thereby be made complete. Lipiodol is often used instead of barium in the x-ray study of duodenal obstruction because there is no danger of its causing obstruction.

Idiopathic intussusception is one of the most frequent surgical emergencies in early life. About 90 per cent of cases occur in male infants between the ages of five and eighteen months. The history is typical in practically all cases and often helps in establishing the diagnosis. A typical history shows a sudden onset of acute abdominal pain in a healthy, vigorous male child. This is followed by the passage of blood and bloody mucus by rectum. The diagnosis is made by palpation of the typical sausage-shaped abdominal mass. It has been wisely stated that every hour over twelve hours that an intussusception remains unreduced decreases materially the surgeon's chances of reducing it. Again, the x-ray diagnosis of intussusception is not necessary and only apt to delay the operation.

Every patient with congenital obstruction of the bile ducts should be operated on as soon as the diagnosis has been made, in the hope that sufficient extrahepatic-duct system is present to make it possible by anastomosis to deliver the bile into the intestinal tract. Unfortunately, enough of the duct system is not present in many cases. Any part of the extrahepatic-duct system may be absent. If there is delay in operation the duct obstruction may cause an extensive cirrhosis of the liver, even though it has existed but a few weeks.

Great progress has been made in the past few years in the surgical treatment of congenital diaphragmatic hernia. This diagnosis may also be made by x-ray study of the chest. Every patient who has either small or large intestine in the chest is a potential candidate for intestinal obstruction — one of the worst complications that can happen in diaphragmatic hernia. These patients should be operated on as quickly as they can be prepared for operation. We have successfully operated on several young infants who were often in such respiratory distress that they were taken to the operating room in an oxygen tent. They were anesthetized, and an intratracheal catheter was inserted, and the operation was carried out without incident.

No discussion of this subject would be complete without mention of the care of inguinal and umbilical hernia and undescended testis — conditions that cause many serious problems in the first year of life. A great many umbilical hernias are found in infants with rickets, and many of them heal spontaneously without operation up to the age of four years. For this reason, operation is not performed — unless the hernia shows signs of incarceration — until the child is four years old. Few umbilical hernias heal spontaneously after that age. Similarly, many congenital inguinal hernias heal

spontaneously during the first year of life. The indication for operation in the first year of life, therefore, is that the hernia becomes incarcerated frequently. After the first year few inguinal hernias heal spontaneously, and the patients should be operated on. The results are excellent, since recurrence in a child is almost unheard of. In my experience many undescended testes do not descend to the scrotum because of a mechanical abnormality, and hormone injections are useless. All patients with undescended testes should be operated on before puberty, since the testicle undergoes its greatest development at that time, and there is much more chance of proper growth if the testicle is in the scrotum when puberty occurs. The ideal age for operation is between eight and twelve years. A Torek operation is done in all cases, since the results are far better than those obtained with other methods.

Acute appendicitis may occur at any age; several cases have occurred in infants under one year of age, and many cases have been observed in adults as old as eighty-eight and ninety years. The history in infants and children is exactly the same as that in adults; in practically all cases the onset occurs with epigastric pain that in about six hours localizes in the right lower quadrant and is followed by vomiting. The temperature is apt to be no higher than 101°F., and the white-cell count is almost always increased to 15,000 or 20,000, with a predominance of neutrophils. Abdominal examination almost always reveals general tenderness and muscular rigidity, but the most important of all abdominal signs is the definite local tenderness over McBurney's point, often accompanied by rebound tenderness. Operation should be done immediately; for delay converts a simple operation into a complicated one. The only point about the operation that I wish to stress is the use of the McBurney incision in all male children and in all female children up to the onset of the menses. After that time one must be more cautious in using the McBurney incision in girls, since many pelvic conditions simulate acute appendicitis and cannot be properly cared for through a McBurney incision. Nothing can overcome the difficulties caused by delay in diagnosis. A child with a ruptured appendix and general peritonitis in the hands of a master surgeon is not so well off as one whose appendix is removed before rupture, perhaps by a surgeon of much less skill. Although I do not like to operate on patients unnecessarily, I believe in giving the child suspected of having acute appendicitis the benefit of the doubt in every case.

Another group of conditions well worth considering is that associated with gross hemorrhage from the intestinal tract in infancy. The first to be mentioned in this category are intestinal polyps, which are often found singly in the rectum but

may be found in any part of the colon. Those in the rectum are almost always palpable on digital examination or at least may be easily found by proctoscopic examination. The diagnosis of polyps higher in the colon may be more difficult, but usually they can be seen on the x-ray film if double contrast mediums are used. Meckel's diverticulum is often the cause of an intussusception or other form of intestinal obstruction but frequently first makes its presence known when the child has a serious intestinal hemorrhage. Meckel's diverticulum often contains gastric mucous membrane that becomes ulcerated, causing serious hemorrhage. Unfortunately, x-ray examination is of no help in the diagnosis of Meckel's diverticulum, which must be made by the exclusion of other possibilities and by surgical exploration. It should not be forgotten that this condition is one of the most frequent causes of gross intestinal hemorrhage in childhood.

Another interesting member of this group is duplication of the small intestine, a potent cause of gross intestinal bleeding. Such duplications are also called enterogenous cysts and are the result of the development of embryonic rests. They are usually found in the terminal ileum at about the point where Meckel's diverticulum occurs, but differ from the diverticulum in that they are found in the mesentery of the intestine that they parallel, whereas Meckel's diverticulum is always found on the antimesenteric border of the intestine. The important thing to remember about duplications is that they are developed in the mesentery and have the same blood supply as the bowel that they parallel but frequently do not have the same type of mucous membrane. They often contain gastric mucous membrane and are the site of hard, indurated, chronic gastric ulcers. Because they have the same blood supply as the bowel, they cannot be removed without compromising the blood supply and therefore necessitate resection with the parallel intestine. Many duplications communicate with the bowel, but others do not. Again, they do not show on the x-ray film but must be seriously considered if the patient has had a gross intestinal hemorrhage.

Duodenal ulcers occur in children but not nearly so often as they do in adults. The diagnosis must never be forgotten, since the ulcer may well be the cause of severe hemorrhage, as in adult life.

* * *

I hope that I have made it clear that abdominal surgery in childhood differs considerably from that in adults and that infants and children are excellent patients for carefully planned and promptly executed abdominal operations. They respond most satisfactorily to gentle handling of their tissues and will recover in spite of the greatest odds if they are given a chance.

ALLERGIC MANIFESTATIONS AFTER THE INJECTION TREATMENT OF VARICOSE VEINS*

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THE treatment of varicose veins by the injection method started in Europe, being used in 1904 by Tavel and in 1912 by Linser. During and after World War I numerous sclerosing agents were employed by Sicard and Gaugier, Montpellier, Genevrier and Dowthwaite, Noul and Troisier. Melkon¹ reviewed the history of the treatment of varicose veins in a paper published in 1929. Since then, various sclerosing agents have been used by many surgeons who gave injections freely and without too much consideration of possible dangers. It is time to call attention to the possible dangers in the use of sclerosing material.

The recent trend in the management of varicose veins is surgical, with high and multiple low ligations and divisions of the long and short saphenous veins and their branches or high and low ligation and stripping of the saphenous veins, and this has eliminated numerous injections; nevertheless, the use of sclerosing agents for postoperative cases, certain types of varicose veins and internal hemorrhoids is still frequent. Various sclerosing agents have been employed in this country, but we speak only of those formerly and at present in use at the New England Hospital for Women and Children and the Mount Auburn Hospital: a 20 to 25 per cent solution of sodium salicylate, an 18 to 25 per cent solution of sodium chloride, quinine hydrochloride and urethane, sodium morrhuate, and Sylnasol. A good sclerosing agent must be safe, effective and painless. Sodium salicylate and sodium chloride solutions, which were first used, were good sclerosing agents and were also safe; they caused cramps after the injection, however. Then, in succession, quinine hydrochloride and urethane, sodium morrhuate and Sylnasol, were employed.

There are numerous references in the medical literature to the allergic reaction of sclerosing reagents. In 1936 Lewis² reported anaphylaxis due to sodium morrhuate, and in 1937 Dale³ reported a reaction to the same drug. Subsequently, Holland,⁴ McCastor and McCastor⁵ and Praver and Becker⁶ described reactions to sodium morrhuate. In 1940 Kadin⁷ stated that these dangers could be eliminated by the routine skin testing of all patients prior to injection. But in 1941 Rosenzweig, Ascher and Zlatkin⁸ reported 938 cases, with reactions in 16 cases, of which 2 gave positive and the other 14 gave negative skin reactions.

The purpose of this paper is to report eight episodes (in 6 patients) of constitutional anaphylactic-like reactions that occurred following the injection of varicose veins with quinine hydrochloride and urethane, sodium morrhuate and Sylnasol. These cases occurred in the twenty years from 1926 to 1945, inclusive. During that time 3037 other patients were treated with no reactions. Most of these allergic reactions occurred in patients who had received injections of sclerosing solutions at intervals of several months. Two patients received quinine hydrochloride and urethane, 3 sodium morrhuate, and 3 Sylnasol. Although three different solutions were injected, the allergic reactions were similar.

The following are brief abstracts of these cases.

CASE 1. M. R., a 32-year-old nurse, was first seen on January 2, 1929, because of pain and cramps in the left leg. There was no history of allergy. Physical examination was negative except for medium-sized varicose veins on both legs. The blood pressure was 110/70.

At weekly intervals 1 to 1.5 cc of quinine hydrochloride and urethane was injected into the varicose veins, and at the end of the 6 weeks all the previously injected veins had been obliterated. There were no constitutional or local allergic manifestations. Four weeks later the patient received 1.5 cc of the same agent. Immediately after the injection she complained of feeling ill and warm. She rapidly went into collapse, the pulse became rapid and weak, the respirations were shallow, and the blood pressure was 40/0. The eyes became congested and puffy, and the pupils were dilated. An urticarial rash appeared on the face and neck and then on the entire body. She complained of severe headache and numbness of the nose and lips as well as belching, nausea and vomiting. She was extremely weak but did not lose consciousness. A subcutaneous injection of 0.5 cc of a 1:1000 solution of adrenalin was given immediately, and the dose was repeated in 30 minutes. Also, 4 cc of spirits of ammonia in water was given by mouth, and cold wet compresses were applied to the forehead. The attack lasted about 1 hour, the pulse, blood pressure and respirations gradually returned to normal. The urticaria began to disappear, and the headache, nausea and vomiting ceased. After resting for 3 hours the patient was allowed to go home. On the next day the patient telephoned that she was slightly weak but otherwise had no symptoms.

Approximately 9 years after the allergic episode, bilateral high ligation and division of the long saphenous vein were done to relieve pain and heaviness of the legs. No further injections were given.

The patient was seen again 7 years later, when examination disclosed a few medium-sized varicose veins above the left external malleolus. On the assumption that she was allergic to quinine hydrochloride and urethane but would be able to take Sylnasol, 0.5 cc of the latter drug was injected after negative scratch and intradermal tests. The scratch test consisted of incision of the skin with a cutting-edge needle just deeply enough to penetrate to the dermis. A drop of full-strength Sylnasol was placed over the area and gently rubbed in, and the area was observed for 15 minutes. Then, 0.1 cc of a 1:10 dilution of Sylnasol was injected intradermally, and the area was likewise observed for 15 minutes. One hour after the first injection a second injection of 0.5 cc of Sylnasol was given. The patient returned in 1 week and received 1 cc of Sylnasol with no reaction. A week later 1 cc of Sylnasol was again injected. Immediately after the injection she had an attack of allergy similar to the

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reaction, 15 years previously, to the quinine hydrochloride and urethane injections

CASE 2. J K., a 40-year-old housewife, was seen on June 14, 1937, because of an ulcer above the internal malleolus of the left leg and marked varicosities on both lower extremities. There was no history of allergy. Physical examination was negative except for the ulcer and the varicose veins. The blood pressure was 118/80.

The patient was advised to have bilateral high and low ligations and divisions of the saphenous veins, but she refused and wished to have the varicose veins injected while she was receiving treatment for the ulcer once a week. At the first visit 1 cc. of quinine hydrochloride and urethane was injected, at the second visit 2 cc., and at the third visit 2 cc. At the fourth visit the previously injected varicose veins were obliterated, and the ulcer was almost healed. A few minutes after the injection of 2 cc. of quinine hydrochloride and urethane the patient began to feel warm and weak. The face and neck became red. Shortly thereafter there was a generalized urticarial rash, the pulse was rapid, the blood pressure fell to 60/0, the respirations were shallow, the eyes were congested and the lids puffy, and the pupils were dilated. Immediately, 0.5 cc. of 1:1000 solution of adrenalin was injected subcutaneously. One teaspoonful of spirits of ammonia in water was given by mouth, and cold wet compresses were applied to the head. The injected leg was lowered, and a tourniquet applied to the thigh for 10 minutes. The attack lasted 30 or 40 minutes. Gradually, the rash began to fade, the pulse, blood pressure and respirations became normal. The patient was allowed to go home after resting for 2 hours. She had no constitutional or local effects on the following day. Three months later bilateral high ligations and divisions of the long saphenous veins were performed. No further injections were given.

CASE 3. W S., a 60-year-old housewife, was admitted to the clinic on August 2, 1940, because of an ulcer on the right leg and varicose veins on both legs. The varicose veins were injected with 10 to 15 cc. of quinine hydrochloride and urethane solution. This was repeated five times at weekly intervals. The patient showed no allergic manifestations.

On March 25, 1945, the patient returned to the clinic. At that visit and again on April 12, April 26 and May 3 she received injections of 10 to 25 cc. of sodium morrhuate. There were no reactions to these injections. Two weeks later, however, a few minutes after the patient had been given an injection of 2 cc. of sodium morrhuate she stated that she felt warm and weak. There were blotches of urticarial rash covering the entire body, the pulse became weak and rapid, and the blood pressure fell to 60/0. Immediately, 1 cc. of a 1:1000 solution of adrenalin was injected subcutaneously. The injected leg was lowered, and a tourniquet was applied at the thigh for 10 minutes. The attack lasted for 30 minutes, after which the pulse and blood pressure gradually returned to normal. The skin rash began to fade, and after resting for 1 hour the patient was allowed to return home by automobile. On the next day she reported that she felt weak and had some pruritus.

CASE 4. J W., a 29-year-old housewife, was seen in the clinic on December 3, 1937, because of cramps in the legs. There was no history of allergy. Physical examination revealed a normal pregnancy of 7½ months' duration and tortuous varicose veins on both legs. The blood pressure was 110/70. Because of the pregnancy she did not receive an injection and elastic stockings were prescribed.

On April 22, 1938, the patient returned to the clinic and a series of four injections of sodium morrhuate were given at weekly intervals. She did not return to the clinic again until January, 1940, when she was given 15 cc. of sodium morrhuate, followed by injections of 15 to 25 cc. of the same drug every 1 to 3 weeks until November 22. At that time, her seventeenth visit since January, 25 cc. of sodium morrhuate was injected in two doses about 2 minutes apart. Immediately following the second injection she complained of pains in the legs, dizziness, weakness and a warm sensation. The pulse was weak and rapid. In about 15 minutes a marked urticaria all over the body and edema of the eyelids and face developed. The patient was given 0.5 cc. of a 1:1000 solution of adrenalin solution, and 15 minutes later received 1 cc. of the same medication. The attack lasted for

1 hour, at the end of that time the urticaria and edema had disappeared.

In 1942 this patient received four injections of sodium morrhuate without a reaction.

On November 5, 1945, the patient again returned to the clinic and was given 1 cc. of Sylnasol. On November 12 she received 2 cc. of Sylnasol, about 2 minutes after the injection she complained of feeling warm, faint and weak. The pulse was rapid and weak, the blood pressure was 80/0. Fifteen minutes after the injection a fine urticarial rash developed on the hands and arms. The patient was given 1 cc. of a 1:1000 solution of adrenalin, followed by 1 cc. of Coramine. The attack subsided in 1 hour. No injections have been given since this reaction.

CASE 5. D L., a 38-year-old housewife, was seen in the clinic on July 30, 1937, complaining of pain in both legs. There was no history of allergy. Physical examination revealed many large varicosities of the entire lower extremities. The blood pressure was 114/70. Bilateral high saphenous-vein ligations were done. During the year the patient received thirteen injections of sodium morrhuate. Seven injections were given in 1938, and three injections in 1941, each consisting of 20 to 35 cc. In 1942 she had eight injections. None of these injections caused any reaction. Three weeks after the dose on June 19, 1942, a ninth injection of 2 cc. of sodium morrhuate was given in two doses. Immediately afterward the patient felt hot and weak, and an urticarial rash developed all over the body. The pulse was barely perceptible, and the blood pressure was 80/40. She was given 1 cc. of a 1:1000 solution of adrenalin. In 1 hour the reaction had largely subsided.

CASE 6. V D., a 36-year-old housewife, was seen on December 7, 1944, because of pain and cramps in the right leg for the previous 5 years. The past history was negative for allergic diseases. She had observed a tendency toward fainting and dizziness on several occasions. She had had phlebitis of the right leg after delivery of a child 7 years previously. Physical examination disclosed a well developed and obese patient. The chest and abdomen were normal. The blood pressure was 110/60. Both legs were covered with large sacular and tortuous varicose veins.

On March 3, 1945, bilateral high and multiple low ligations and divisions of the saphenous veins were done. Two weeks later after a negative skin test, four injections of 1 to 2 cc. of Sylnasol were given at weekly intervals. Most of the varicose veins were obliterated, and the leg pain and cramps disappeared. There were no constitutional or local reactions. On November 30, 1945, when the patient returned for a follow-up examination, there were a few small varicose veins on the anterior aspect of the right leg. Injections of 15 cc. of Sylnasol were given in two places. One week later 2 cc. of Sylnasol were injected in three places. A few minutes after the injection the patient felt warm, weak and dizzy. A red rash appeared over the entire body. The pulse became weak and rapid and was hardly perceptible. There was moderate dyspnea. The blood pressure was 40/0. The eyes became congested, and the lids puffy. The patient complained of a severe headache and had nausea and vomiting. A subcutaneous injection of 0.5 cc. of a 1:1000 solution of adrenalin was given, and this dose was repeated in 20 minutes. A tourniquet was applied to the thigh for 10 minutes, and 1 cc. of Coramine was injected subcutaneously. The attack lasted for 1 hour, and then all subjective and objective symptoms gradually disappeared. After resting for 4 hours the patient was allowed to go home by automobile. On the next day she was up and around, but still rather weak.

* * *

In this series of cases the constitutional and allergic reactions occurred with dramatic suddenness. None of the patients had had a history of allergic manifestations, such as asthma, hay fever and urticaria. Two patients gave four negative skin tests, in the other 4 the skin tests were not done. Most of the patients had received injections of sclerosing solutions at preceding intervals of a few

months or more. Most of the severe reactions occurred after a temporary cessation of treatment, and in all cases the allergic manifestations appeared within one to five minutes after an injection. The patients had urticarial rash and were warm and weak, with rapid pulse, low blood pressure and puffy congested eyes, and in 2, nausea and vomiting occurred. None of the patients lost consciousness. The patients with the lowest blood pressures appeared to have the severest reactions. Two patients had allergic shock from quinine hydrochloride and urethane, 3 from sodium morrhuate, and 3 from Sylnasol. The symptoms were the same regardless of the drug used.

There are many theories concerning the phenomena of anaphylaxis and allergy. Of these, one has been advanced by Sir Thomas Lewis,⁹ who assumed that the union of antigen and antibody in the tissues caused an irritation in or on the cells of the tissues, with the resulting liberation of a histamine-like substance that produced the physiologic effect characteristic of anaphylaxis or allergy. Zimmerman¹⁰ believed that sclerosing solutions may mix with the liver protein and produce allergic reactions. A theory has been advanced that hemolysis occurs, contact of the susceptible patient's blood with the solution resulting in liberation of a protein substance that causes the reaction. K. M. Lewis² suggests that sodium morrhuate acts as a hapten and sensitizes susceptible persons, particularly if they have received an injection one or two weeks previously. Crip¹¹ states that a patient may become hypersensitive to the drug if more than seven or ten days elapse between injections. Drug allergy is not identical with protein allergy, since the development of sensitivity appears to be dependent on the combination of the drug with a body protein. The

exciting agent in true anaphylaxis is always a soluble protein. In acquired allergy, this is not necessarily so, for many nonprotein substances, such as drugs, are capable of acting as allergens.

It seems probable that the substance released from the union of antigen and antibody in the cells of the tissue is a histamine-like substance that either acts directly as a vasodilator on the smooth muscles of the small vessels or depresses the vasoconstrictor sympathetic nerves, thus increasing the permeability of the arterioles and producing a generalized skin rash and a low blood pressure.

SUMMARY

Eight attacks of allergic manifestations in 6 patients following the injection treatment of varicose veins are reported, and the possible explanations for these reactions are briefly discussed.

REFERENCES

- 1 Melkon E. A. Treatment of varicose veins by injection method. *New Eng J Med* 200:690-694, 1929.
- 2 Lewis K. M. Anaphylaxis due to sodium morrhuate. *J A M A* 107:1298, 1936.
- 3 Dale, M. L. Reaction due to injection of sodium morrhuate. *J A M A* 108:718, 1937.
- 4 Holland G. A. Reactions from sodium morrhuate in sclerosing of varicose veins. *Canad M A J* 41:262, 1939.
- 5 McCastor, J. T. N., and McCastor M. C. Reaction to sodium morrhuate injections for varicose veins and hydrocele. *J A M A* 109:1799, 1937.
- 6 Prayer, L. L., and Becker, S. W. Sensitization phenomena following use of sodium morrhuate for chemical obliteration of varicose veins. *J A M A* 104:997, 1935.
- 7 Kadin M. Sodium morrhuate severe reaction to injection. *J Michigan M Soc* 39:561, 1940.
- 8 Rosenzweig, S., Ascher, M. S. and Zlatkin L. Varicose veins and allergic reactions in injection treatment. *J Michigan M Soc* 40:800-806, 1941.
- 9 Lewis T. *Blood Vessels of the Human Skin and Their Responses*. 322 pp. London: Shaw & Sons, 1927.
- 10 Zimmerman, L. M. Allergic like reactions from sodium morrhuate in obliteration of varicose veins. *J A M A* 102:1216, 1934.
- 11 Crip, L. H. *Essentials of Allergy*. 381 pp. Philadelphia: J. B. Lippincott Co. 1945.

MEDICAL PROGRESS

RUBELLA (GERMAN MEASLES)*

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AT THE annual meeting of the Ophthalmological Society of Australia in 1941 Gregg¹ reported a series of congenital cataracts in 78 cases following attacks of rubella in the early months of pregnancy. Since then, numerous studies have been made regarding the prenatal influence of this disease with results indicating that the fetus may suffer a variety of defects leading to serious congenital malformations or that the fetus may be destroyed in utero with consequent miscarriage or stillbirth. Thus it is that a disease hitherto considered to be of little consequence and to require only differentiation from other exanthems has become a serious problem in obstetrics, medicine and public health. It is the purpose of this review to look backward through the history of rubella, to sum up the present knowledge of its pathogenesis, and to consider the numerous problems with which we are now confronted.

TERMINOLOGY

According to Emminghaus² rubella was first described by two German physicians, de Bergen in 1752 and Orlov in 1758. There followed numerous others who called attention to its manifestations under various terms but eventually under the title of *Roetheln*. This term was used both in England and in America, and it is under this heading in the first series of the *Index Catalogue of the Library of the Surgeon General's Office*. Owing to the early interest displayed by German writers and the acceptance of the term *Roetheln*, this disease came to be known as "German measles." In 1866 Henry Veale³ introduced the term "rubella," which is now accepted in English-speaking countries, and one to be encouraged for the simple reason that this disease is not a German form of measles or any other form of measles, but rather a distinct entity unto itself.

The terminology of rubella in different countries has been and still is a cause of confusion. The trouble lies in the historical background. The early German writers considered it to be a modified form of either measles or scarlet fever. Schönlein⁴ regarded it as a hybrid of both and gave it the name "rubeola" to distinguish it from "morbilli" or true measles. Eventually, rubeola came to be used to designate measles, but to this day *Rubeola* is used in Sweden and *rubéola* in Spain for rubella. In

France the term is modified to *rubéole*, and even in Austria *Rubeolae* is sometimes used in place of *Roetheln*. Consequently, in investigation of the literature, or in conversation with foreigners, it is necessary to keep these synonyms in mind.

While German authors wrangled over the relation of rubella to measles and scarlet fever, Willan,⁵ in England, described the condition as *rubeola sine catarrho* and remarked that "persons receiving the miasm in this form are peculiarly liable to a second attack of measles." In the next year, 1814, Maton⁶ in a paper read before the Royal College of Physicians described rubella as a disease entity. In 1840 Paterson,⁷ "unaware of any description of this disease in our language," entered into a historical review and proceeded to confuse it with scarlet fever and measles, citing among his cases a number of fatal ones. In 1940 an editorial in the *Edinburgh Medical Journal*⁸ entitled "One Hundred Years Ago" took Paterson's remark at its face value to the neglect of Maton's excellent observations.

John Homans,⁹ a president of the Massachusetts Medical Society, is credited with being the first physician in America to describe rubella. This he did in an unpublished paper before the Boston Society for Medical Improvement on April 14, 1845. Cotting,¹⁰ who was present at this meeting, presented a paper on the same subject in 1853 before the Norfolk District Medical Society. This was incorporated in a subsequent address delivered twenty years later, constituting the earliest published account of the disease in the United States. At that time an active interest in the disease had sprung up in this country, headed by J. Lewis Smith,¹¹ who contributed to the symposium on rubella at the International Medical Congress in London in 1881 — the only occasion on which this disease ever received so much attention. The interest culminated in the two classic works by Atkinson¹² and Griffith¹³ in 1887, and that of Corlett¹⁴ in 1902. A characteristic article of this period was written by Townsend¹⁵ in 1904. This author withdrew his previously expressed skepticism of the identity of rubella and described an epidemic in Boston, with a description of his cases. A comprehensive account was given by Schamberg and Kolmer¹⁶ in 1928. Throughout this era attention was given to establishing the entity of rubella, its symptomatology and course, and its differentiating characteristics. Nowhere in the literature prior to

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1941 have I been able to find any trace of evidence that rubella in the course of pregnancy is a source of danger to the fetus. The latest extensive paper covering rubella appears in Christian's *Oxford Medicine*.¹⁷

ETIOLOGY

The causative agent of rubella is a filterable virus. In 1938 Steinmaurer¹⁸ claimed to have demonstrated the virus with the fluorescent microscope and to have isolated it on the chorioallantois of the egg embryo, but the evidence presented is by no means convincing. Hiro and Tasaka¹⁹ collected physiologic saline washings of the nasopharynx during the eruptive stage. The filtrate was injected subcutaneously into a group of 16 nonimmune children convalescing from chronic disease, of whom 4 exhibited a characteristic rubella rash, and 2 showed typical lymphadenopathy without any skin eruption. The incubation period was seven days in 3 cases, and eight, eleven and seventeen days in the others. Habel²⁰ used similar nasal washings obtained within twelve to twenty-four hours after the appearance of the rash. The filtrate was introduced by the intranasal, subcutaneous, intraperitoneal and intravenous routes into *Macaca mulatta* monkeys. Washings obtained from patients on the third day of the disease yielded negative results, whereas those obtained on the first day gave equally positive results from all four routes, although the monkeys did not always exhibit a rash. Habel also reported successful cultures on the chorioallantoic membrane of the chick embryo, although no specific pathologic lesions were found.

DISTRIBUTION

Rubella is widely distributed, being found in North and South America, Europe, Africa, Asia, Japan and Australia. Unlike measles it does not appear to be unusually severe when it first strikes on virgin soil.

AGE

Rubella, like measles, is rare in the first six months of life. Corlett¹⁴ remarks that "infants have contracted the disease a few days after birth." Measles is usually mild when it occurs at that time, and therefore rubella, if proportionately mild, might easily be missed. I have collected reports of 5 mild cases in infants ranging from eighteen days to two months old.¹⁷ After six months of age rubella takes its usual course, which being milder than measles and of shorter duration is frequently not reported. In fact, a physician may not even be called. In children's institutions the disease spreads freely. Thus, Michael²¹ reported 80 cases among 199 children, of whom all those under six years of age contracted the disease. Humphrey and Ekermeyer²² found that 48 per cent of the children exposed were attacked, whereas Geiger²³ observed

an attack rate of 12 per cent among school children. Thus, it appears that in children's institutions rubella exhibits a fairly high attack rate, whereas among day-school children the rate as reported is low. To a certain extent this can be explained as failure in reporting the day-school cases. On the other hand, the rather high incidence of rubella among young adults in colleges and in military life suggests the possibility that more children escape rubella than they do measles. Contagious hospitals usually have more cases of rubella among young adults than among children. This is due to the fact that rubella is not generally hospitalized except when the cases arise in dormitories or barracks. The disease rarely attacks those over forty years of age. Simpson,²⁴ however, has recently reported a case in an epidemic at Dorset, England, in which the patient was eighty-two years old.

INCUBATION PERIOD

Maton,⁶ Emminghaus,² Thomas,²⁵ Earle²⁶ and Pospischil²⁷ all arrived at the approximate figure of eighteen days for the incubation period. Many authors have been content to compile figures given by previous writers along with the addition of their own observations, until 41 series are listed by Schamberg and Kolmer¹⁶ without references and without any discrimination regarding possible faulty diagnoses easily detected in the original sources. As such, these compilations are not only worthless but also misleading. From a single three-hour exposure to the onset of the eruption exactly eighteen days elapsed in a case reported by Lindberg.²⁸ This figure is confirmed by a chart presented by Aycock and Ingalls²⁹ of an epidemic at a boys' boarding school.

PERIOD OF INFECTIVITY

Since it is now apparent that the virus of some of the acute exanthems resides in the upper respiratory tract during the prodromal period and the height of the eruptive stage, their spread occurs during the prodromal period before a diagnosis has been established and isolation carried out. In measles the predominant catarrhal symptoms with sneezing and coughing cause the air about the patient to be filled with virus-laden droplets. Chicken pox, without such catarrhal symptoms, however, is spread presumably from the upper respiratory tract prior to the eruption.^{30, 31}

Isolation of the virus of rubella from the upper respiratory tract during the first forty-eight hours of the eruption^{19, 20} lends support to the contention that rubella is spread from the upper respiratory tract. Griffith¹³ observed that 63 of his patients in children's institutions contracted the disease in spite of prompt and careful isolation of all cases with the appearance of the rash. Consequently, the period of infectivity appears to precede the eruptive phase. Furthermore, it is highly probable that

with the fading of the rash the period of infectivity terminates as in measles. This is supported by Habel's²⁰ negative results from nasal washings taken on the third day of the disease and his demonstrations of the virus in the blood of patients bled within twelve, twenty-four and thirty hours of the onset of the rash, but not in blood taken on the third day. Since the rash is often of relatively short duration, isolation precautions established after the appearance of the rash are merely attempts to control the spread during the last part of the period of infectivity. In the light of the available evidence, Geiger's²¹ recommendation that cases be isolated for the duration of palpable lymph nodes is hardly tenable, particularly since the postauricular nodes may remain swollen for an indefinite period. Consequently, isolation beyond the period of the eruption is of doubtful value.

IMMUNITY

A lifelong immunity to rubella is usually established by an attack. Late second attacks have been recorded, however.²² Just how this permanent immunity is established and in what manner it is lost is one of the great problems of virology²³ and cannot be entered into here. Relapses occur and are not to be confused with late second attacks, which are rare. Griffith¹⁸ reported a relapse in 3 cases, once on the eleventh day and twice in the third week. Humphrey and Ekermeier²² observed relapses in 19 of 305 cases (6.2 per cent). The relapse, which was usually milder than the original attack, occurred in the third week in 15 cases, in the fourth week in 3, and on the forty-first day after the original attack in 1. These authors are of the opinion that the establishment of immunity is often delayed, allowing reinfection through subsequent exposure during this period of partial immunity. A number of factors may enter into the mechanism of this phenomenon, which I have observed on rare occasions at the Haynes Memorial. Probably the reason I have seen this so rarely is that the patients admitted with rubella during my term of service were discharged before a relapse could take place. On the other hand, when rubella had broken out on a scarlet-fever ward, the patient was sometimes detained because of scarlet-fever complications long enough to suffer a relapse from rubella. In such cases the relapse was identical in severity with the first attack.

COURSE

Rubella is generally considered to be the mildest of the exanthems. For the most part the patient complains of no discomfort throughout the course of the disease.

In children under observation in a hospital ward a slight rise in the temperature during the twenty-four hours preceding the eruption may be the only prodromal sign. In adults the prodromal symptoms

are in proportion to the severity of the subsequent eruption. In the severer cases among adults prodromal fever, headache, muscular aches and pains and the characteristic enlargement of the lymph nodes have been encountered. Anorexia, nausea and vomiting are rare.

The blood picture in the prodromal stage is of peculiar interest. A marked leukopenia is sometimes observed, both in children and in young adults, but this phenomenon is by no means constant. On two occasions, however, we have correctly suspected the diagnosis prior to the eruption through known exposure and white-cell counts of about 2000. In the eruptive stage this leukopenia is apt to shift to a lymphocytosis, along with the appearance of a few monocytes. Careful blood studies by Lindberg²⁴ failed to yield any blood findings of diagnostic value because of the wide variability. Hynes²⁵ carried out serial white-cell counts on 61 adult patients; these generally showed an absolute leukopenia at the onset, changing to an absolute lymphocytosis on the sixth day and a neutrophilic leukocytosis after ten days. These findings offered no difference from those observed in measles. During the first week an increased sedimentation rate was observed in a quarter of his cases.

At the Haynes Memorial Hospital 1046 patients have been admitted for rubella. Only 5 of these were admitted prior to the beginning of my term of service, and I was one of them — rubella being the only disease that I have acquired from my work at this hospital. Besides these admissions there have been a number of outbreaks of rubella in the convalescent scarlet-fever wards. None of these patients suffered any serious complications, with the exception of 2 who were admitted with rubella encephalitis and 1 mild case of encephalitis that developed six days after the onset. One patient in the third month of pregnancy miscarried spontaneously on the sixth hospital day. The bulk of the adults were college students, patients referred from the armed forces, student nurses and interns from our own and other hospitals.

The exanthem may be ushered in by a brilliant generalized erythema of the face, as noted by Pospischill.²⁷ This lasts for only twelve to twenty-four hours and precedes the severer types of rash. More frequently, the eruptive stage begins with the appearance of small, pale, rose-pink macules that come out first on the face and scalp and spread downward over the trunk and extremities. In the severer cases the macules may coalesce in certain areas, especially over the lower back and buttocks. Only in severe cases are macules found in the axillas, the popliteal spaces, the palms and the plantar surfaces. The severer the eruption, the longer it remains, and in the severe type a coppery tint may appear as in scarlet fever. Such cases may be accompanied by considerable fever and may be followed by a furfuraceous desquamation of the face

and trunk as the rash subsides Schamberg and Kolmer¹⁶ describe an unusual case in a twenty-seven-year-old nurse with severe prodromal symptoms of fever, chilliness, headache, vomiting and cervical lymphadenopathy that lasted for five days. The macules first appeared below the knees and spread upward, with many crescent formations. Vomiting and fever persisted. The face was finally involved on the third day, and the rash disappeared on the sixth day. The incubation period had been only thirteen days. This case reminds one of the severest type of smallpox, *variola purpurica*, in which the incubation period is greatly shortened.

In general the macules remain discrete. There are, however, several outstanding characteristics of the disease.

The eruption comes out suddenly on the face, from which it tends to fade rather abruptly in the milder cases, so that on the second day the rash begins to fade from the face, although it is then well marked over the trunk.

The eruption tends to be kaleidoscopic or, as some authors put it, polymorphous. The first term is more appropriate, since the eruption may be macular at first and may then assume a more punctate appearance. Thus, the rash may resemble measles on one day and scarlet fever on the next. The fading of the rash from the face on the second day may suggest scarlet fever, which only rarely involves the face.

Catarrhal symptoms are absent unless due to a secondary infection, such as the common cold.

Conjunctivitis is not constant, but when present is characteristic in that the orbital conjunctivas are involved, giving a suffused pink to the whites of the eyes. This is in marked contrast to the definite palpebral conjunctivitis seen in measles. Photophobia is extremely rare, lachrymation is absent, and there is none of the purulent sticky discharge frequently seen in measles.

Lymphadenitis is particularly characteristic over the mastoid region. These postauricular lymph nodes may be so enlarged as to be not only palpable but also visible from a distance. Klaatsch³⁴ mentions that on this symptom alone the diagnosis of rubella may be ventured in the dark. In such cases a child may complain of "earache" without any evidence of otitis media, whereas in other cases with similar enlargement of the lymph nodes there is neither pain nor tenderness. The postauricular nodes, however, are not always affected, and the absence of enlargement need not preclude the diagnosis of rubella. Moderately enlarged suboccipital and posterior cervical chains of lymph nodes are frequently palpable, as in measles. Furthermore, there may be generalized prominence of the lymph nodes in the axillas and groins. The

enlargement of the postauricular nodes may persist for weeks and even for years.

Fever is sometimes entirely absent. Often, a slight fever extends from the prodromal period through the height of the eruption. In the severe cases there may be chilliness and a temperature as high as 104°F, but for the most part such patients are rarely as uncomfortable as those with proportionately severe measles or scarlet fever.

Forchheimer,³⁵ of Cincinnati, is responsible for much of the confusion that exists regarding the appearance of the throat in rubella. In 1898 he described the enanthem as small "rose red spots" on the soft palate and uvula that fade away within twenty-four hours, "sometimes leaving a yellowish brown pigmentation." In another article he³⁶ refers to the enanthem as "small, discrete, dark red, but not dusky papules which disappear in a short time, leaving no trace behind." These diverse descriptions were advanced at the time when Koplik had given his classic account of the throat lesions in measles, which have come to be known throughout the world as "Koplik spots." Consequently, writers on rubella began to refer to "Forchheimer spots." Authors are apt to spell the name incorrectly when they depict the spots according to one or the other of Forchheimer's versions. At times, an author remarks that he has also observed something quite different, whereupon he describes the other condition, entirely ignorant of Forchheimer's other version. The fault seems to lie with Forchheimer, who failed to clarify his position. The fact is that the enanthem if present is fleeting, and is sometimes kaleidoscopic in character like the exanthem. I have had occasion to demonstrate to students both versions as well as perfectly normal looking throats in the course of rubella. Humphrey and Ekermeier²² failed to find an enanthem in any of their 305 cases. In my opinion there is nothing pathognomonic about the appearance of the throat in rubella. Bennett and Copeman³⁷ reported pharyngitis, follicular tonsillitis, congestion of the nose "without catarrh" and soreness of the gums in a severe epidemic in the British Expeditionary Forces. Todd³⁸ also noted the same soreness of the gums in her own case, "as though her teeth were falling out."

The appearance of the tongue also lacks any diagnostic significance. At times the bright strawberry tip may be observed, but the subsequent prominence of the papillae over the entire surface—frequent in scarlet fever—is never present. Pospischil³⁷ and Lindberg²⁸ have remarked on the difficulty sometimes presented in differentiation of the tongue of rubella from that of scarlet fever. I can share this view only so far as to say that the tongue early in mild scarlet fever, as in rubella, often appears to be perfectly normal.

The spleen is sometimes palpable just as it is in some of the other common virus diseases, such as mumps and measles

UNUSUAL FORMS

Rubella ecchymotica has been described by Ström,³⁹ of Stockholm. This author discusses 2 cases in adults in which the enanthem and exanthem were distinctly ecchymotic in character. Aside from these ecchymoses there was no loss of blood. The patients were not acutely ill, and the blood findings were normal. This type of eruption, which I had occasion to observe in some of the sailors referred from the Coast Guard, as well as in several college students, is due to a lowered capillary resistance. The character of inflammation in the acute exanthem is dependent on the nature of the toxic material present, and it is only by the outward manifestations that the diagnosis of the various exanthems of virus origin can be made. Landis⁴⁰ states that the permeability of the capillary endothelium is increased in all types of inflammation. The degree of inflammation brought about is further dependent on the amount of virus present and the spreading factor, both of which influence the resistance offered by the capillary epithelium. In rubella the exhibition of an ecchymotic character in the eruption implies a soil in the skin and mucous membranes that allows greater inflammation with greater permeability of the capillary endothelium but without necessarily augmenting the constitutional toxicity, provided other organs are not involved. These ecchymoses are responsible for the coppery hue that accompanies the fading of a severe eruption alluded to above.

Modified rubella, like modified measles, implies a minimal attack in which the eruption is barely visible or never seen. The diagnosis is established in these cases by the characteristic lymphadenopathy with or without fever, by the circumstantial evidence of exposure with an appropriate incubation period and sometimes by the added confirmation of transmission of the infection to other persons. Lindberg²⁸ reported such a case without a rash in which the postauricular lymph nodes were markedly prominent. Flöystrup⁴¹ reports the case of his own son, who, after a definite exposure in school, exhibited characteristic lymphadenitis, conjunctivitis, vomiting and slight fever, with only a few pale macules on the cheeks lasting but a few hours. The boy's younger brother, however, contracted a typical attack of rubella from this exposure. The title used by Flöystrup, "rubella without a rash," is misleading, and the case has been used as an example of rubella without a rash, which it is not. Habel²⁰ reports 2 cases of rubella without a rash, 1 of which is misleading. We have seen measles modified in newborn infants and by the late administration of convalescent serum or gamma globulin when the eruption was exceedingly slight and fleeting. There-

fore, although rubella may be modified through high resistance to a point where no rash occurs, it is also possible for a rubella rash to be so fleeting as to escape the observation of the attending physician — just as authors in quoting Flöystrup's case have failed to note that an eruption did take place.

DIFFERENTIAL DIAGNOSIS

The greatest difficulty in the diagnosis of rubella has occurred in the differentiation of this disease in its mildest form from modified measles after the late administration of convalescent serum or gamma globulin. One must lean heavily on the circumstantial evidence of exposure, because the usual catarrhal symptoms of measles, as well as Koplik spots, may be absent. Measles with Koplik spots should never present any difficulty.

A mild scarlet fever can make trouble, especially if the patient with rubella is seen on the second or third day when the rash has disappeared from the face and is punctiform. Scarlet fever does not give a rash on the face, except on the forehead and temples. When it does so the eruption is rough and feels like coarse sandpaper over the forehead, and usually is accompanied by a severe rash over the trunk with all the earmarks of scarlet fever. In rubella the throat may be inflamed from heavy smoking or from some secondary infection. At the onset of mild scarlet fever there may be no lymphadenitis, or if present it will be manifested in the anterior cervical chain in contrast to rubella, which involves the postcervical chain and the suboccipital and postauricular lymph nodes. As pointed out above, the tongue at the onset of scarlet fever may not have taken on the characteristic enlargement of the papillae. The kaleidoscopic character of the rubella rash is always helpful. A mild scarlet fever does not always desquamate, but the characteristic late peeling under the fingernails means that the patient has had scarlet fever, no matter how much the disease appeared to be rubella.

In the course of infectious mononucleosis a scattered, pinkish, macular eruption may come out over the trunk and extremities but, unlike rubella, is rarely marked on the face. The fever is apt to be much more prolonged. In the first few days the blood picture in infectious mononucleosis may not differ from that at the onset of rubella, but monocytes will appear in increasing numbers. Moreover, there may be a severe faucial angina with white fibrin deposit. Positive heterophil agglutination tests later on will confirm the diagnosis. A case of complete temporary heart block has been recorded as coming on in rubella, but the case as described might have been infectious mononucleosis.⁴²

Erythema infectiosum is most frequently found in Central Europe and is rare in England and America. The incubation period is from five to ten days.⁴³ The eruption appears first on the face, especially on the cheeks, as a papuloerythema, and

then on the extensor surfaces of the extremities, reaching the trunk last of all. The lesions are polymorphous, sometimes morbilliform or scarlatiniform in appearance and, according to Rolleston and Ronaldson,⁴⁸ often tend to be annular or gyrate. There is little or no fever and no lymphadenopathy. Eosinophilia is usually present, and the eruption persists for ten days.

Roseola infantum (exanthem subitum) is not to be confused with rubella. This disease occurs in infants, is attended with a high fever lasting three or four days and is often associated with convulsions. The laboratory findings are essentially normal. Slight generalized lymphadenopathy may be present, but the postauricular lymph nodes are not enlarged. The disease terminates with an abrupt drop of the temperature to normal and the appearance of a rubella-like eruption that promptly fades. The rickettsial diseases, such as typhus and Rocky Mountain spotted fever, may exhibit macular eruptions not unlike those of rubella. Even though no hemorrhagic lesions occur the constitutional symptoms are severe and persistent.

Late serum rashes associated with generalized lymphadenopathy are sometimes confused with rubella. But wheals are apt to develop, as in a generalized nettle rash. Drug eruptions, particularly from the sulfonamides, barbitol derivatives and quinine, lack the kaleidoscopic course of rubella. As in the conditions mentioned above, circumstantial evidence is of great importance. Erythema multiforme is differentiated by the prominence of the early eruption on the extremities and the circinate character of the lesions. The irregular form of rubella described by Schamberg and Kolmer¹⁶ and cited above under the discussion of the rubella exanthem certainly demands careful consideration of the circinate type of erythema multiforme.

COMPLICATIONS

Aside from the damage done in early pregnancy, the complications of rubella are exceedingly rare. As in other virus diseases, the menstrual cycle may be disturbed. It may be delayed or brought on early according to our experience, but such disturbance is infrequent. A mild form of polyarthritis may follow a few days after the eruption has disappeared. Lindberg²⁸ observed this in 6 cases. The knees and feet were involved in 3 cases among children, and the fingers in 3 adult cases. A mild fever accompanied these joint involvements. Potter,⁴⁴ however, describes a polyarthritis in a woman that appeared on the third day of the eruption and involved the wrists and fingers, as well as the knees, ankles and feet, and was unaccompanied by any fever. Geiger²³ reported 36 cases of arthritis in approximately 180 cases of rubella in Arkansas. Simpson²⁴ reported polyarthritis of a mild migrating type in 25 of 72 patients with rubella in England, and Bennett and Copeman³⁷ noted this complication

in the British Expeditionary Forces in the same year. Gregg¹ states that many of the cases of rubella in the epidemic of Australia in 1940 and 1941 showed "rheumatic sequelae." Gölzow⁴⁶ reported a case of pancreatitis during the acute stage, accompanied by severe diarrhea and general abdominal pains, along with a rise in the blood diastase.

Thrombopenic purpura in the course of rubella has been reported in 10 cases. Pitten⁴⁶ gives an account of a case in a nine-year-old girl with no previous history of bleeding. There was thrombopenia with a prolonged bleeding time. Gunn⁴⁷ describes the case of a nine-year-old girl with a previous history of mild nosebleeds since the age of five but with no cutaneous manifestations. This case also showed a thrombopenia with a prolonged bleeding time, but the white-cell count rose to 13,000 with 79 per cent neutrophils. In both cases there was severe and protracted epistaxis with cutaneous purpuric lesions on the trunk and extremities. The spleen was not palpable in either case. Bleeding stopped in both on the sixth day, and uneventful recovery followed. Gunn⁴⁷ cites 4 other cases reported in the literature. During 1946 a total of 4 new cases of thrombopenic purpura were reported. Warren, Rogland and Potsubay⁴⁸ report 2 severe cases among soldiers at Fort Dix, both of whom gave negative family and past histories of bleeding tendencies. One followed two days and the other four days after the onset of rubella. Epistaxis, bleeding from the gums, gross hematuria, intestinal bleeding and a palpable spleen were present in both cases. Diminished platelet counts of 30,000 and 40,000 were found. In 1 case the platelets completely disappeared at one time, and the count remained as low as 62,000 at the end of fifty days. In both there was a prolonged bleeding time (30 minutes), as well as generalized petechiae over the skin. A complete recovery followed in five months in one case and in two months in the other. Fox and Walton⁴⁹ report 2 mild cases in children. The first occurred in a nine-year-old girl ten days after the onset of a mild case of rubella. The second was in a sixteen-year-old boy, occurring on the fifth day of a rubella that had begun with a temperature of 103°F. Thus, the severity of the rubella attack had no relation to the incidence of thrombocytopenia. In the first case the platelet count was 40,000, the bleeding time was over 45 minutes, and the petechiae were distributed over the body. In the second case the platelet count and bleeding time are not given, but red cells were found in the urine. The petechiae developed rapidly and spread over the entire surfaces of the extremities. The first patient recovered in three weeks, and the second in two weeks. The family histories and the past histories regarding bleeding tendencies were negative.⁵⁰

Rubella encephalitis has attracted considerable attention. It usually comes on between the second and the sixth day after the onset of the rash, and

it may be manifested as a mild meningoencephalitis or as an encephalomyelitis. Thus, the symptoms range all the way from headache and rigidity of the neck to coma and convulsions. There may be diplopia, bulbar palsies, thickness of speech, muscle twitching, weakness of the extremities and retention of urine. Merritt and Koskoff⁵¹ reported 4 cases, Barracough⁵² 2; Davison and Friedfeld⁵³ 6, and Jack⁵⁴ 1. Wingo⁵⁵ reported a case in a twenty-four-year-old woman who developed signs of meningeal irritation seven days after the onset of the rash. The spinal-fluid pressure was equivalent to 240 mm of water, and examination of the fluid revealed 40 lymphocytes per cubic millimeter. Diplopia appeared on the third day of this complication and persisted for four days. Bradford⁵⁶ described 2 cases of rubella meningoencephalitis from a British Naval Hospital, both of which showed a spinal-fluid count of 20 cells per cubic millimeter, with a marked preponderance of lymphocytes. One patient recovered in two weeks, and the other in three weeks.

Margolis, Wilson and Top⁵⁷ reported 14 cases of post-rubella encephalomyelitis that occurred in Detroit in 1942. They estimated that encephalomyelitis occurred at the rate of 1/6000 cases of rubella. This rate is not unlike that found in measles and chicken pox. In mumps, on the other hand, a benign meningoencephalitis occurs in approximately 10 per cent of cases when carefully looked for, whereas encephalomyelitis is exceedingly rare. These authors do not differentiate cases of meningoencephalitis from encephalomyelitis. Six of their 14 cases were mild and showed neurologic signs for only three days. There were 8 severe cases, in 4 of which the patients died. In these 4 fatal cases the patients did not survive for more than three days. Among those who recovered, 1 showed symptoms for eight days, 1 for ten days, and 1 for over one hundred and twenty days, the last had almost recovered when the paper was written, however. The spinal-fluid pressure was found to be equivalent to from 120 to 180 mm of water, and the cell counts varied from 8 to 500 per cubic millimeter, averaging 91, with mononuclears predominating. The authors present a protocol that includes their own 14 cases, as well as 37 others culled from the literature, with a combined mortality of 21 per cent.

A unilateral temporary retrobulbar neuritis with diminished vision in the affected eye has been reported by Owen and Greenway⁵⁸. This occurred in the course of "meningoencephalitis" developing five days after rubella in a twenty-six-year-old man. This was really an encephalomyelitis with inability to urinate for seven days. The headache lasted for four and a half days, but aside from these symptoms the patient was not extremely sick and was all well on the sixteenth day. Revilloid and Long⁵⁹ report a case of "polyneuritis" in an eight-year-old boy that developed ten days after rubella. There were

diplopia and marked weakness of the muscles of the extremities, with loss of tendon reflexes. Complete recovery followed in a few weeks. This case also appears to belong under encephalomyelitis. Hodges and Witner⁶⁰ report a total of 15 cases of neuritis following rubella, of which 3 were brachial.

The pathology of rubella encephalitis is described by Davison and Friedfeld⁵³. Autopsy disclosed perivascular infiltrations in the gray and white matter of the cortical convolutions, the brachium pontis, the superior cerebellar peduncle, the dentate nuclei, the cerebellum and the brain stem. In this respect the pathology does not differ from other encephalomyelitides.

The origin of the encephalopathies is unknown. One theory held by many is that some latent encephalomyelitic virus is aroused into activity by the virus of rubella. In support of this is the similarity of the symptoms, signs and pathology found in the rubella type and the types that follow measles, chicken pox and vaccinia. On the other hand, Putnam⁶¹ lays great emphasis on the vascular occlusions with thrombosis, which, according to him, form the basis of the pathologic lesions. In his opinion it is possible that some sort of allergic reaction associated with the establishment of immunity takes place whereby the clotting mechanism is disturbed. At any rate, the inflammatory reaction in the brain is not simultaneous with lowered capillary resistance in the skin, because the encephalitic manifestations appear not with the onset of the eruption but usually as it is subsiding or after the rash has entirely cleared up.

RELATION TO SECONDARY INFECTIONS

Although any concurrent infection may occur during or after rubella it does not appear that this disease in itself tends to predispose to other infections. This statement does not agree with the opinion of Hamburger,⁶² who presents charts from an Army hospital to support his contention that patients recovering from rubella show the same well recognized susceptibility of measles patients to streptococcal infections. His experience may well be due to the prevalence of streptococci in that hospital. I have reviewed 100 cases of rubella that occurred among patients convalescing from scarlet fever. There was no evidence of increased susceptibility to any of the complications incident to streptococci in their respective age groups. This is in marked contrast to measles in the convalescence of scarlet fever in which the incidence of suppurative otitis media is greatly increased in all age groups.⁶³

Humphrey and Ekermever,⁶⁴ reporting an epidemic of 305 cases of rubella in children, found tonsillitis in 15 cases, suppurative otitis media in 3 and suppurative cervical adenitis in 2. The last two complications are not given in relation to the tonsillitis. One is led to assume that all three complications were the result of a concomitant beta-

hemolytic streptococcus infection of a nonscarlet-fever-producing strain. In any event, the incidence of 1 per cent otitis media reported in this series is far lower than that found among children with scarlet fever or measles, to say nothing of a combination of the two. Florand and Fiessinger⁶⁴ described a case of streptococcal septicemia occurring six days after rubella. Bronchitis and laryngitis have been observed during the course of rubella, but in such cases these complications existed well before the onset of the eruption and were contracted independently of the rubella but were in no way enhanced by the disease. Indeed, it is safe to say that rubella does not offer any added danger to concomitant infections or pre-existing disease, with the exception of thrombopenic purpura and possibly a latent encephalitic infection.

(To be concluded)

REFERENCES

- Gregg, N. M. Congenital cataract following German measles in mother. *Tr Ophth Soc Australia* 3:35-46, 1941.
- Emminghaus H. Über Rubeolen. *Jahrb f Kinder* 4:47-59, 1870.
- Veale, H. History of epidemic of Rötheln, with observations on its pathology. *Edinburgh M J* 12:404-414, 1866.
- Schönlein. Cited by von Hebra, F. *On Diseases of the Skin, including the Exanthemata*. Vol. 1. Translated and edited by G. H. Fagge. 396 pp. London: The New Sydenham Society, 1866. P. 166.
- Willan. Cited by Gregory, G. *Lectures on the Eruptive Fevers*. 258 pp. London: Henry Renshaw, 1843. P. 102.
- Maton, W. G. Some account of rash liable to be mistaken for scarlatina. *M Tr, Roy Coll Physicians* 5:149-165, 1815.
- Paterson, R. Account of Rötheln of German authors, together with few observations on disease as it has been seen to prevail in Leith and its neighborhood. *Edinburgh M & S J* 53:381-393, 1840.
- Editorial. Hundred years ago German measles. *Edinburgh M J* 47:702, 1940.
- Homan, J. Rötheln. *Boston Society for Medical Improvement. Records of Meetings* (manuscript). Vol. 5, June 24, 1844 to May 8, 1848. 370 pp. Boston: Medical Library.
- Cotting, B. E. Rötheln—German measles. *Boston M & S J* 88:485-488, 1873. (Record before the Roxbury Medical Club, March 26, 1863. Incorporated in this article is the original paper as read before the Norfolk District Medical Society in September, 1853, a second epidemic having come under his observation twenty years later.)
- Smith, J. L. Contributions to study of Rötheln. *Tr Internat M Cong* 4:14-21, 1881. *A Treatise on the Diseases of Infancy and Childhood*. Seventh edition. 900 pp. Philadelphia: Lea Bros & Co., 1890. P. 328.
- Atkinson, I. E. Rubella (Rötheln). *Am J M Sc* 93:17-34, 1887.
- Griffith, J. P. C. Rubella (Rötheln German measles) with report of one hundred and fifty cases. *M Record* 32:11-17 and 37-41, 1887.
- Corlett, W. T. *A Treatise on the Acute Infectious Exanthemata, including Rubella, Scarlatina, Rubella, Parvella, and Vaccinia, with Especial Reference to Diagnosis and Treatment*. 392 pp. Philadelphia: F. A. Davis Co., 1902. Pp. 348-371.
- Townsend, C. W. Concerning German measles. *Boston M & S J* 150:403, 1904.
- Schramberg, J. F., and Kolmer, J. A. *Acute Infectious Diseases*. Second edition. 888 pp. Philadelphia: Lea & Febiger, 1928. Pp. 545-573.
- Wesselhoef, C. Rubella. *Christian's Oxford Medicine* (in press).
- Steinmauer, H. Virusanzeichen bei Rubeolen, Parotitis epid und Stomatitis aphosa. *Monatsschr f Kinderh* 75:98-102, 1938.
- Hiro, Y., and Tasaka, S. Die Röteln sind eine Viruskrankheit. *Monatsschr f Kinderh* 76:328-332, 1938.
- Habel, K. Transmission of rubella to *Macacus mulatta* monkeys. *Pub Health Rep* 57:1126-1139, 1942.
- Michael, M. Rubella report of epidemic of eighty cases. *Arch Pediat* 25:598-606, 1908.
- Humphrey, T. F., and Ekmeyer, E. W. Rubella report of epidemic with unusual number of complications and relapses. *Ohio State M J* 33:406-408, 1937.
- Geiger, J. C. German measles in city adjacent to Army cantonment and its probable relation thereto. *J A M A* 70:1818-1820, 1918.
- Simpson, R. E. H. Rubella and polyarthritis. *Brit M J* 1:830, 1940.
- Thomas, L. Neue Erfahrungen über Rötheln. *Jahrb f Kinderh* 5:345-355, 1871-1872. Rubella (Rötheln, German measles). In *Cyclopaedia of the Practice of Medicine*, Edited by H. von Ziemssen and A. H. Buck. Vol. 2. New York: William Wood & Co., 1875. Pp. 129-148.
- Earle, C. W. Rötheln. *St Louis M & S J* 41:392-394, 1881.
- Pospischill, D. Über Rubeolae und Doppelreanthem. *Jahrb f Kinderh* 59:723-776, 1904.
- Lindberg, G. Beiträge zur Nosologie der Rubeola. *Acta Paediat. Scand* 1:1-19, 1924.
- Aycock, W. L., and Ingalls, T. H. Maternal disease as principle in epidemiology of congenital anomalies with review of rubella. *Am J M Sc* 212:366-379, 1946.
- Goodpasture, E. W. Comments on virus diseases and their control. *South M J* 30:731-735, 1937.
- Evans, P. Epidemic of chickenpox. *Lancet* 2:339, 1940.
- Wesselhoef, C. Virus disease from clinical point of view. *M Clin North America* 30:1009-1023, 1946.
- Hynes, M. Leucocyte count in rubella. *Lancet* 2:679, 1940.
- Klaatsch, A. Über Rötheln. *Ztschr f klin Med* 10:114, 1885.
- Forchheimer, F. Enanthem of German measles. *Tr Am Pediat Soc* 10:118-128, 1898.
- Idem. German measles (Rubella). In *Twentieth Century Practice of Medicine*. Edited by Thomas L. Stedman. Vol. 14. 602 pp. New York: Wm Wood & Co., 1898. Pp. 177-188.
- Bennett, R. A., and Copeman, W. S. C. Notes on rubella, with special reference to certain rheumatic sequelae. *Brit M J* 1:924-926, 1940.
- Todd, D. M. Rubella. *Brit M J* 1:718, 1940.
- Ström, J. Hämorrhagische Form von Rubeola (Rubeola ecchymotica). *Acta med Scandinavica* 105:160-169, 1940.
- Landis, E. M. Capillary circulation. In *Colloid Chemistry Theoretical and Applied*. Edited by J. Alexander. Vol. V. *Theory and Methods, Biology and Medicine*. 1256 pp. New York: Reinhold Publishing Co., 1944. P. 916.
- Flöystrup, G. Rubella without rash (rubella sine exanthemate). *Brit J Child Dis* 20:20-23, 1923.
- Logue, R. B., and Hanson, J. F. Complete heart block in German measles. *Am Heart J* 30:205-207, 1945.
- Rollleston, J. D., and Ronaldson, G. W. *Acute Infectious Diseases. A handbook for practitioners and students*. Third edition. 477 pp. St. Louis: C. V. Mosby Co., 1940. Pp. 360-363 and 392.
- Potter, O. Severe forms of rubella. *Brit M J* 2:1084, 1930.
- Gülzow, M. Pancreatitis bei akuten Exanthemen Scharlach Maseren, Röteln. *Klin Wochenschr* 18:353-356, 1939.
- Pitten, T. Über einen Fall von symptomatischen Morbus Werthof nach Röteln. *Arch f Kinderh* 86:114-121, 1929.
- Gunn, W. Case of rubella complicated by purpura haemorrhagica. *Brit J Child Dis* 30:111-117, 1933.
- Warren, H. D., Rogland, F. T., and Pottsday, S. F. Thrombocytopenic purpura following rubella. *M Clin North America* 30:401-404, 1946.
- Fox, M. J., and Walton, W. P. Thrombocytopenia complicating rubella. *Marquette M Rev* 11:208-210, 1946.
- Fox, M. J. Personal communication.
- Merritt, H. H., and Koskoff, Y. D. Encephalomyelitis following German measles. *Am J M Sc* 191:690-696, 1936.
- Barracough, W. W. German measles encephalomyelitis. *Canad M A J* 36:511-513, 1937.
- Davison, C., and Friedfeld, L. Acute encephalomyelitis following German measles. *Am J Dis Child* 55:496-510, 1938.
- Jack, R. D. S. Rare complication of German measles. *St. Berik. Hosp J* 1:135, 1940.
- Wingo, S. M. Encephalomyelitis complicating rubella: report of case. *U S Nav M Bull* 45:546, 1945.
- Bradford, R. I. C. Two cases of rubella meningo-encephalitis. *Brit M J* 1:312, 1943.
- Margolis, F. J., Wilson, J. L., and Top, F. H. Post-rubella encephalomyelitis: report of cases in Detroit and review of literature. *J Pediat* 23:158-165, 1943.
- Owen, A. B. S., and Greenway, T. M. Meningoencephalitis complicating German measles. *M J Australia* 2:536, 1940.
- Revilhod, E., and Long, U. Cas de polyneurite à la suite de la rubeole. *Rev med de la Suisse Rom* 26:50, 1906.
- Hodges, G. M. W., and Witney, E. W. Neuritis following rubella. *Brit M J* 1:830, 1940.
- Putnam, T. J. Newer conceptions of postinfectious and related forms of encephalitis. *Bull New York Acad Med* 17:337-347, 1941.
- Hamburger, M. Jr. Studies on transmission of hemolytic streptococcus infections. I. Cross infections in Army hospital wards. *J Infect Dis* 75:58-70, 1944.
- Wesselhoef, C. Factors influencing incidence and course of otitis media in scarlet fever. *Ann Int Med* 12:1473-1485, 1939.
- Florand, A., and Fiessinger, N. Septicémie benigne à streptocoques endopéricardite à streptocoques à la suite d'une rubeole. *Bull mém Soc med d hâp de Paris* 45:1452, 1921.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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CASE 33251

PRESENTATION OF CASE

A twenty-three-year-old single woman entered the hospital complaining of blueness of the hands, face and feet.

No abnormality at birth or in development as a child had been noted, but her mother stated that as a child she had not played with other children very much and had always been "lazy." At the age of twelve a mild, dull pain in the chest, located to the left of the lower portion of the sternum, had been noticed. At that time a bluish discoloration of the face and hands was first observed. There were no associated symptoms that seriously incapacitated the patient, although she noticed that if she exercised as other children she had headaches and became blue and somewhat weak. These symptoms, however, did not prevent her from roller skating and dancing. The pain disappeared promptly, but occasionally thereafter she was aware of a slight, dull pain in the chest, without particular relation to any activity. In addition, she complained that the eyes frequently became "blood-hot" and that the cold aggravated the blueness of the extremities. A gradual clubbing of the fingers from that time was noted. Three years before admission the patient went to a physician with these complaints. She was told that she had a low blood pressure and was given some "pills," which she took without benefit, she did not, however, consider the symptoms severe enough to return. A year later she saw a dentist for bleeding gums and was referred to her physician for a blood examination, which was negative. Fourteen months before entry she attempted to join the WAVES and was told that everything was normal except for blueness, clubbing of the fingers and an abnormal chest film. She was referred by the Navy to a sanatorium, where extensive studies for tuberculosis were negative. At the time of admission the patient complained only of cyanosis and clubbing of the fingers and toes. She felt perfectly well, being able to exercise strenuously without ill effect other than an increase in cyanosis, which she thought had gradually become more prominent.

The past history revealed no serious illness. The patient had had mumps, measles and chicken pox

as a child. She had had occasional sinusitis and a chronic morning cough productive of a teaspoonful of sputum. The gums had always bled easily. There was no history of familial disease.

Physical examination on admission revealed a well developed and well nourished girl in no distress. There was a striking cyanosis of the face, hands and feet with severe clubbing of the fingers and toes. The conjunctivas were markedly congested, and examination of the fundi showed extremely dilated veins with tortuous arterioles. The throat was a dusky red. There were no abnormal pulsations in the neck. The chest was clear. The heart was normal in size. The pulmonic second sound was louder than the aortic second sound. No murmurs were heard. One examiner described an inconstant pulmonary systolic murmur. The liver and spleen were not palpable. The extremities showed good pulsations. Neurologic examination revealed a right knee jerk that was less active than the left.

The temperature was 99.6°F, the pulse 80, and the respirations 15. The blood pressure was 100 systolic, 80 diastolic, in the right arm and 95 systolic, 78 diastolic, in the left.

Examinations of the blood showed red-cell counts ranging from 7,100,000 to 8,790,000, with hemoglobins of 21.5 to 24.9 gm., and a white-cell count of 12,000, with a normal differential. The venous blood had an oxygen content of 16.7 and an oxygen capacity of 28.5 vol per cent, with a hematocrit of 69.7 per cent. The arterial blood had an oxygen content of 24.85 and an oxygen capacity of 27.7 vol per cent, with a hematocrit of 67 per cent. The oxygen saturation was 89.2 vol per cent. The circulation time with ether was 11 seconds and with Decholin, 23 seconds. The vital capacity was 3100 cc. Urinalysis was normal. An electrocardiographic tracing was normal.

X-ray examination of the chest revealed an extensive "flecky" area of increased density in the right middle lobe, mainly in the anteromedial segment (Fig 1). There was also a fine network of increased density in the left lung field laterally that was thought to be in the lingular portion of the left upper lobe. Both leaves of the diaphragm were well defined and showed good motion. The hilar shadows were normal. The heart was normal in size, shape and action. Fluoroscopy showed evidence of pulsations of the major branches of the right pulmonary artery somewhat farther away from the hilus than usual. The finer branches showed no abnormal pulsations. The hands and feet failed to show any evidence of pulmonary osteoarthropathy.

The patient's condition remained unchanged. On the sixteenth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR EARLE M CHAPMAN. A pulmonary murmur was heard. Does that mean that it was heard over

the lung or in the second left interspace? That is an important observation, and it needs clarification

DR RONALD C SNIFFEN The record is not clear on that point

DR CHAPMAN May we see the x-ray films?

DR STANLEY M WYMAN The film of the chest shows mottled density lying in the anterior medial segment of the right middle lobe as seen in the anteroposterior projection. It is seen in the lateral view lying in this triangle. There was said to be fine mottling in the lingula of the left upper lobe

making a diagnosis of an arteriovenous fistula of the lung, with secondary polycythemia

Only two other conditions have to be considered in the differential diagnosis, and they are congenital heart disease and polycythemia vera. The latter is excluded by the failure to find immature white cells or basophilia in the smear. Congenital heart disease is practically excluded by the entirely normal cardiac findings.

This rare disorder is often congenital but possibly traumatic in origin, and yet the few cases reported

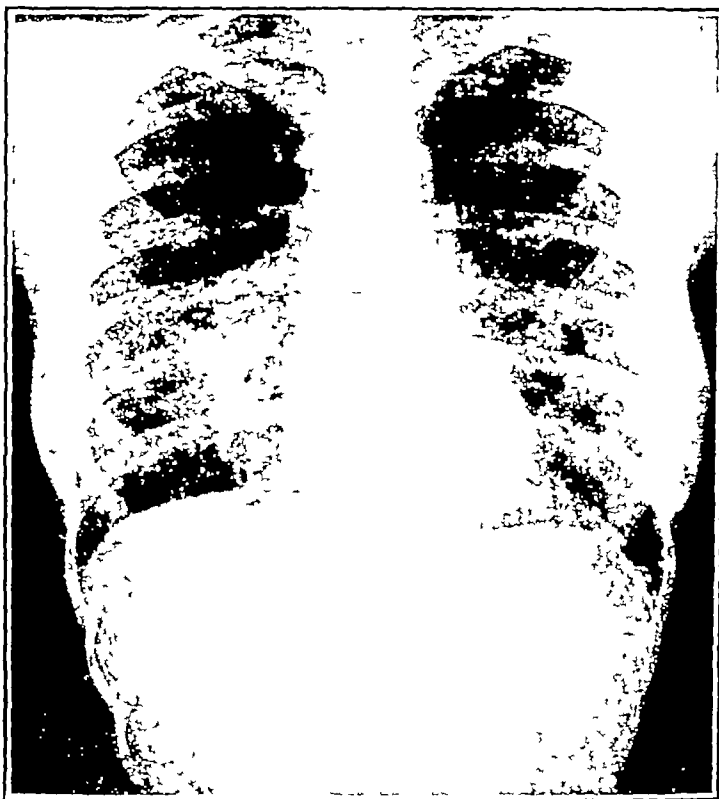


FIGURE 1

I cannot be sure of that finding. I think it should be noted that there is a rounded, sharply defined shadow extending outward and downward at this point, coming down to this region, which suggests the pulmonary artery. The lateral view of the skull shows no definite abnormality.

DR CHAPMAN May I ask if pneumothorax was done and if a further definition of the mass was obtained?

DR SNIFFEN Pneumothorax was not done.

DR CHAPMAN This case represents a rare clinical syndrome that would not have been correctly diagnosed or treated ten years ago. Indeed, its diagnosis was missed on three occasions during the patient's life. The characteristics are so clearly set forth in this history that I have no hesitancy in

in the literature since 1938 seem to have established a group of symptoms and signs that should indicate the correct diagnosis. These are cyanosis, clubbing of the fingers and toes, and symptomatic polycythemia usually in a young person with a normal heart and an obscure pulmonary lesion by x-ray study. Some patients have a continuous murmur over the lesion if it is of the cavernous type connecting with the pulmonary artery.

The hazards of continuing with the lesion are that it may rupture and lead to sudden death in pulmonary hemorrhage, such as in the case described by Rodes¹ in 1938, which at autopsy showed three hemangiomas in the right lung and one in the left lung, or the patient may be incapacitated by the symptoms of anoxemia. Such were the

symptoms that led to the first successful removal of the right lung containing such a hemangioma in 1942

Since then several cases have been successfully operated on, and the patients have lost the cyanosis immediately after operation, the blood counts have returned to normal, and the symptoms have disappeared. Disappearance of the symptoms, however, depends on removal of the entire lesion and the absence of multiple arteriovenous fistulas.

There are some interesting data and clinical points in this case that I think deserve further comment. For instance, the bleeding of the gums and suffusion of the eyes and mouth are clinical signs consistent with a polycythemia, and yet they seem to have been overlooked as diagnostic signs. The pulse rate was slow, and this suggests that the cardiac output was normal, since according to Marey's law, a rapid pulse can be due to a low blood pressure and not to an increased venous pressure.

Having seen the x-ray film I place the lesion in the right lung rather than the left, although it is possible for such a lesion to exist on the left side as well.

Fluoroscopy showed, "evidence of pulsations of the major branches of the right pulmonary artery." That is why I was concerned with the so-called "pulmonary murmur" and with the decision whether it was a murmur over the heart. The history stated that no heart murmurs were heard and later that a "pulmonary murmur" was heard. To me, that means a murmur over the lungs. This sign has been described in some cases of arteriovenous fistula of the lung.

The oxygen saturation in itself could be a significant diagnostic procedure. The patient had a slightly slow circulation time, with an arteriovenous lung fistula or even in pulmonary congestion one could expect even greater delay in the blood circuit through the lung.

In conclusion, then, I believe that this case is characteristic possibly of a cavernous hemangioma type of arteriovenous fistula of the lung, and I assume that at operation perhaps all or part of the right lung was removed. It would be interesting to hear from others about the subsequent course.

DR SNIFFEN: Dr King, have you any comment?

DR DONALD S KING: The patient came to the sanatorium with a diagnosis of questionable tuberculosis and was sent to this hospital from there.

DR JOHN T QUINBY: I believe that I was the first to see the patient in the Out Patient Department with some of the fourth-year men, and I thought that she had congenital heart disease. I followed her after entry into the hospital. Preoperatively the hematocrit was 67 per cent and the oxygen saturation 89 vol per cent.

DR SNIFFEN: Is such cyanosis usual with a not very low oxygen saturation?

DR QUINBY: As I understand it, the cyanosis depends on concentration of the reduced hemoglobin. With a high total hemoglobin, an unsaturation of 6 or 7 per cent apparently leaves enough reduced hemoglobin to cause a dusky color. Another interesting problem is that the cyanosis and exertion limitation were progressive as the patient grew older, suggesting that the magnitude of the lesion was increasing.

DR CHAPMAN: I intended to comment on the presence of cyanosis. The oxygen saturation was low, — the normal figure should not be under 95 vol per cent, and in this case it was 89, representing slight diminution, — but this was compensated for by the polycythemia. In most patients with congenital heart disease when one third of the blood is shunted through from the venous to the arterial side, the reduced hemoglobin goes up from 1 to 4 vol per cent, and cyanosis becomes established. It is unfortunate that the volumes per cent of reduced hemoglobin were not available.

CLINICAL DIAGNOSIS

Hemangioma of lung

DR CHAPMAN'S DIAGNOSIS

Arteriovenous fistula of lung, with secondary polycythemia

ANATOMICAL DIAGNOSIS

Cavernous hemangioma of right middle lobe of lung

PATHOLOGICAL DISCUSSION

DR RICHARD H SWEET: As Dr Chapman has said, this is a characteristic entity. The correct diagnosis was made ahead of time in this case by the Medical Department and concurred in by the surgeons. At that time there had been only four or five such cases operated on successfully, at least according to reports in the literature. All of them, I believe, had been pneumonectomies with the exception of one patient of Dr Janes in Toronto. This case, which was bilateral, was successfully operated on in two stages. The case under discussion was a characteristic so-called "hemangioma," which I prefer to call an arteriovenous fistula. There was one enormous pulmonary artery, probably as large as the whole pulmonary artery should be normally, and there was a corresponding enormous vein, which led out from the middle lobe. In the middle lobe there were numerous dilated vascular channels. So far as I know this is the first case treated by lobectomy alone. Since then, by the way, we have had a similar case — a lesion in the middle lobe — in a child two years of age, who presented the same clinical picture and was cured by surgery. On visiting Dr Alexander's Clinic in Ann Arbor I recently discovered that there was a third such case with arteriovenous fistula in the middle lobe. It had been thought to be the first

one that had been resected because we had not published our two cases

DR SNIFFEN After removal the external surface of the right middle lobe showed a number of small blebs without pleural reaction. Three large vessels entered the lung at the hilus. One of these vessels followed the course of the anteromedial bronchus, and 2 cm beyond its origin it was broken up into a honeycomb of large anastomosing, vascular channels that occupied an area 9 by 4 by 3.5 cm in the medial

operated on suffered alarmingly of exsanguinating hemorrhages on the operating table. I therefore assume that the rapid reduction was due to blood loss. We are sensitive to that, and this patient did not suffer any appreciable loss of blood during the operation. I think that possibly this was responsible for the slow return of the hemoglobin to the normal level.

DR HOWARD B SPRAGUE Certainly, in peripheral arteriovenous communication, one would expect

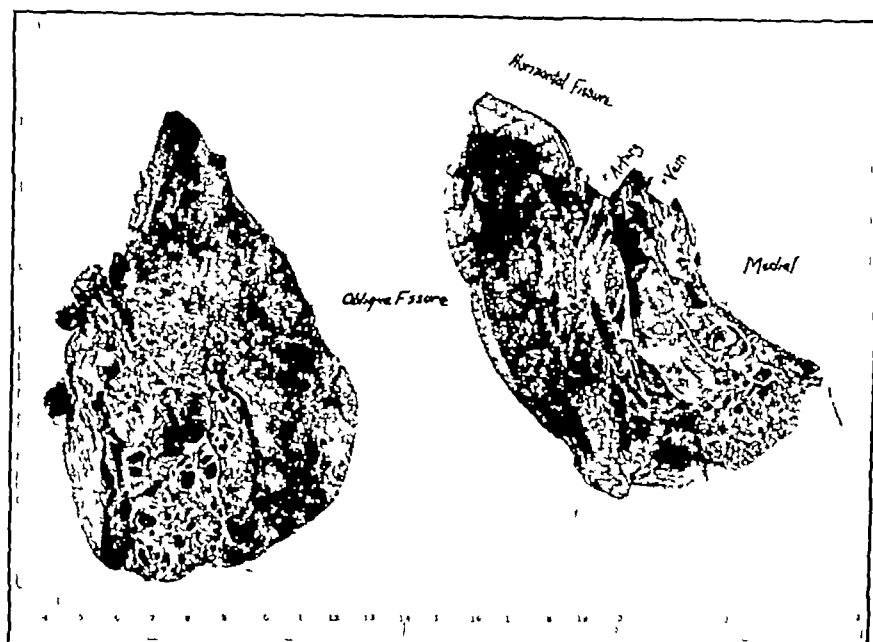


FIGURE 2

portion of the lobe and accounted for the blebs on the external surface (Fig 2). The lesion was not encapsulated but showed no evidence of growth. The channels were lined by endothelium, with localized points of subendothelial fibrous thickening.

The postoperative findings are of some interest. Eight days after operation the hematocrit had fallen to 62 per cent, and the oxygen saturation was up to normal. The hemoglobin remained elevated. In the few cases that I have read about, such as the patient studied by Hepburn and Dauphinee,² the blood values, including the hemoglobin, had returned to normal in eight days. In the case under discussion about six months elapsed before the hemoglobin and red-cell count fell to normal figures.

DR SWEET Several months after operation the patient showed some reduction in the clubbing of the fingers, and she was no longer cyanotic. I think that one comment is of interest regarding Dr Sniffen's remark about the rate at which the hemoglobin returns to a normal level. Until this operation was done, — I have not followed the reports in the literature since then, — all the patients

enlargement of the heart because of the increased flow. We have to agree possibly to an increase in pulmonary venous pressure. Does it not mean that the right ventricle can stand increased circulation better than the left ventricle? There are so few of these cases that we have not been able to draw a conclusion, but I think that it is of considerable interest that this patient had an increase in flow.

DR SNIFFEN Another point in reference to Dr Chapman's remarks: it is stated in the record that the blood examination two years before admission was normal in this case. In Hepburn's case the patient had been followed carefully in a sanatorium, and at that time she had a normal red-cell count and hemoglobin. Only in the last year and a half did the hemoglobin and the red cells increase.

DR SWEET How about cyanosis?

DR SNIFFEN It was present.

DR SWEET When the blood counts were normal?

DR SNIFFEN Yes, presumably because of the arteriovenous shunt and before secondary polycythemia had become established.

DR CHAPMAN I should suggest that the lesion was expanding in type and becoming enlarged and that the degree of polycythemia was in relation to the size of the shunt. In this case, as the tissues became distended, there was more bleeding. It is an interesting point that Dr Sprague has made, and one that has been made in other cases. It is surprising how the heart can accommodate itself to this extra load.

REFERENCES

1. Rodes C. B. Cavernous hemangiomas of lung with secondary polycythemia. *J A M A* 110 1914, 1938
2. Hepburn, J., and Dauphinee J. A. Successful removal of hemangioma of lung followed by disappearance of polycythemia. *Am J M Sc* 204 681-685 1942

CASE 33252

PRESENTATION OF CASE

A forty-nine-year-old stock clerk entered the hospital because of increasing difficulty in swallowing.

Six years before entry the patient had begun to have attacks of diffuse abdominal pain associated with nausea and vomiting and occurring at any time of the day or night, without relation to meals or to the type of food eaten. A "stomach operation for ulcers" performed at a local hospital had brought considerable relief of symptoms, but he continued to have some epigastric distress and occasional nausea and vomiting despite "ulcer diets." Eighteen months before entry he had a sudden attack of extremely severe abdominal pain, radiating to the right shoulder. He was rushed to a hospital and operated on for "perforated ulcer." The site of rupture was found with difficulty owing to adhesions from a previous rupture. The postoperative diagnosis was "duodenal ulcer." Six months before entry the patient began to complain of food "sticking in the throat" accompanied by a pain in the substernal region that he had never had before. These symptoms gradually increased in severity until three or four months before entry, when he became unable to take solid food except with great difficulty. Two weeks before entry, the patient consulted another physician, who had x-ray films taken and told him that he had a "growth deep in the chest." The dysphagia continued to progress until at the time of entry the patient could take "only coffee", everything else was regurgitated. He had lost about 25 pounds in the previous three or four months. He was in the habit of taking one or two alcoholic drinks and smoking ten or fifteen cigarettes daily.

Physical examination revealed a thin, pale man who had obviously lost weight. The voice was hoarse. He complained of pressure in the epigastrium, causing discomfort in the midsubsternal region. The heart, lungs and abdomen were clear.

The temperature was 100°F, the pulse 98, and the respirations 35. The blood pressure was 100 systolic, 80 diastolic.

Examination of the blood showed a hemoglobin of 12.2 gm and a white-cell count of 9100, with 65 per cent neutrophils. The nonprotein nitrogen was 23 mg, and the serum protein 4.6 gm per 100 cc, and the chloride 94 milliequiv per liter. A blood Hinton test was negative. The urine was normal.

A barium swallow revealed marked obstruction to the flow of thin barium in the midesophagus, caused by an oval, sharply defined mass, measuring 5 cm in length. The mass was attached primarily to the anterior and left lateral wall of the esophagus and involved a large part of the wall (Fig 1). No definite ulceration was seen. Small amounts of barium trickled slowly past the mass, but this was insufficient to fill the stomach for a satisfactory examination of that organ. The stomach appeared irregular in outline, and its folds were markedly swollen. There was no evidence of gastric resection. It was not possible to determine the presence of a gastroenterostomy. The duodenal cap was large and showed a large crater. There was no definite evidence of disease in the chest. The medial wall of the left main bronchus was poorly outlined.

An operation was performed.

DIFFERENTIAL DIAGNOSIS

DR CHESTER M. JONES There is a remote possibility of a single diagnosis in this case, but I do not believe that one diagnosis can cover all the symptoms. The diagnosis of duodenal ulcer would explain the symptoms for the first five and a half years before entry. The patient was operated on twice, and ulcer was found. There were symptoms of perforated ulcer eighteen months before entry, with pain in the right shoulder of subphrenic origin, a duodenal ulcer was said to have been found. I suspect that the surgeon merely did a simple closure at that time. I believe that the patient had a duodenal ulcer.

Certain things are not clear about that diagnosis, particularly in relation to the symptoms, which never followed a typical ulcer pattern. The symptom that brought the patient to this hospital was difficulty in swallowing of short duration — six months. He had pain with the difficulty in swallowing, with substernal reference of pain, which is ordinarily accurate and usually localizes the level of the lesion. The fact that there was pain suggests ulceration, because stenosis alone causes fullness and regurgitation rather than pain.

On physical examination the patient had lost weight and the voice was hoarse, indicating at least a possibility of involvement of the recurrent laryngeal nerve, which suggests involvement outside rather than inside the esophagus. If this statement of hoarseness is correct and if the sign was of recent origin it should be taken into serious account. The patient had fever, again suggesting an ulcerating

process or a condition causing some inflammation of pulmonary tissue

The laboratory data are noncontributory except for a total protein of 4.6 gm per 100 cc, which I regard as simply the figure that one would expect from starvation

The x-ray films should be the source of information that will give us the clue to the probable diag-

proves it. Small amounts of barium trickled slowly past the mass, and although the examination of the stomach was not entirely satisfactory the organ appeared irregular in outline and its folds were markedly swollen. Whether that means that the x-ray men suggested that the patient had carcinoma of the stomach, I do not know. I should like to see the films. Obviously if a gastroenterostomy had



FIGURE 1

nosis. I am not under any delusions about the difficulty of making a correct diagnosis in this sort of case. I do not believe that it is necessary to make a correct diagnosis, and I suggest that what is most important is the decision to make a move to relieve the obstruction, whether or not the diagnosis is correct is entirely beside the point. On the other hand I realize that I am here to try to make a diagnosis, and I should like to register surprise that the x-ray examination as described showed midesophageal narrowing due to an oval lesion, which was sharply defined, measured 5 cm in length and was attached primarily to the anterior and left lateral wall. No definite ulceration was seen. That certainly suggests that there was not an ulcer, but I do not believe that it absolutely

been done six years before entry it was done for insufficient reason. The second operation was a closure, and therefore the x-ray film probably did not show anything diagnostic. The x-ray description is that of a large duodenal cap with a large crater. If there was a crater, there should have been an active duodenal ulcer, and I do not see how one can define it otherwise. Even if the ulcer was active, I do not see how it had anything to do with what was going on in the esophagus.

The question arises whether there was an intraluminal tumor involving the esophagus, whether it arose from the wall of the esophagus or whether it was entirely extraluminal, pressing on the esophagus. There is at least a remote suggestion in the last sentence of the x-ray report that the medial wall

of the left main bronchus was poorly outlined, also, the patient was hoarse, which may suggest extrinsic pressure on the left recurrent laryngeal nerve. I might add that I heard Dr Sweet recently discuss mediastinal tumors, and if I remember the diagnostic batting average from x-ray films was about 10 per cent correct, or 90 per cent incorrect, from the point of view of preoperative diagnosis. Is that right?

DR RICHARD H SWEET Yes

DR JONES I do not expect to do well from the x-ray films

DR SWEET That was a selected group, I might add

DR JONES This case is also selected

DR STANLEY M WYMAN There is either a crater in the duodenal cap or a pseudodiverticulum from the old ulcer. I did not fluoroscope the patient, but the film is consistent with a crater.

DR JONES We have no lateral films here. The trachea is in the midline. There is no displacement of the heart, and I do not know whether there is compression of the left bronchus in that area. Certainly, there is an obvious tumor, which again is interesting because of the magnitude of the defect. But it is not constant, and it seems to me that there is pressure rather than an annular constriction, which one ordinarily sees with an adenocarcinoma of the esophagus. The stomach shows simply a picture of what is ordinarily considered a gastritis with thick rugal folds.

I should say that this was a tumor that was not intraluminal. I do not believe that it was carcinoma of the esophagus. On reading the history my first impression was that of esophageal cancer. I do not believe that the patient had an esophageal ulcer—a lesion that occurs at a lower level. This may have been a tumor arising in the wall of the esophagus with barium coming down on one side. Perhaps it was intraluminal.

DR WYMAN In this area the mass presses in on the column of barium, the barium flowing to the right. One must consider a mass arising in the wall of the esophagus as well as something pressing on the esophagus. I do not want to mislead Dr Jones. Perhaps I have said something I should not have said.

DR JONES You apparently helped me, but I need it. The point I make is that wherever one looks here there is evidence of esophageal wall on the right side and not on the left, which suggests compression where the barium runs through. It may arise from the wall of the esophagus itself. If that is the case, I suspect that it would go beyond the outer wall of the esophagus and encroach on the structures out here, possibly involving the recurrent nerve. I shall say that this was an in-

trinsic tumor of the wall of the esophagus, and I should not be surprised to find it slightly ulcerated.

CLINICAL DIAGNOSIS

Carcinoma of esophagus

DR JONES'S DIAGNOSIS

Tumor of esophagus arising from submucosal tissues

ANATOMICAL DIAGNOSIS

Leiomyoma of esophagus

PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY Dr Sweet, will you tell us your findings?

DR SWEET Dr Jones gave an able discussion of this case. We were greatly puzzled by the severity of the symptoms. The x-ray appearance suggested more a benign tumor of the intramural type than a carcinoma of the esophagus. We were prepared from the history, as Dr Jones has said, to find that the patient had carcinoma of the esophagus, and then the x-ray films puzzled us. We likewise did not make any connection between this and the ulcer. Dr Richard Schatzki said that although he could not examine the stomach wall, there was something peculiar about the stomach, and he suspected carcinoma of that organ. We thought that the patient might have a carcinoma or lymphoma of the stomach, and we were going to investigate further. That had nothing to do with the esophageal tumor. At operation it looked like leiomyoma.

The tumor bulged through the musculature but it was easily removed locally. A myomectomy was performed. A biopsy had been performed previously in the muscular wall, and there was a point where I had to enter the lumen because the mucosa was so adherent. A portion of mucosa had to be excised with the tumor. I ought to say that it is extremely unusual for benign tumor of the esophageal wall to cause as much obstruction as this patient had.

A PHYSICIAN Why did he have pain?

DR SWEET Because he was so obstructed. The esophagus was almost completely shut off.

DR MALLORY Microscopical section showed a spindle-cell tumor, which we diagnosed as benign leiomyoma of the esophageal wall.

DR JONES Did the tumor press on any structures outside the esophagus?

DR SWEET No.

DR JONES What did you do with the stomach?

DR SWEET I think we shall take care of that some time soon, if the patient continues to show evidence of neoplasia there.

The New England Journal of Medicine

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STREPTOMYCIN TREATMENT FOR TUBERCULOSIS

It was not long after streptomycin had been shown to have antibiotic activity against a variety of gram-negative and gram-positive bacteria, including *Mycobacterium tuberculosis*,¹ that experiments designed to determine its efficacy in experimental tuberculosis were undertaken. The first preliminary results in guinea pigs, which were reported by Feldman and Hinshaw,² indicated that streptomycin was well tolerated in these animals and that, even with the rather small doses and the short course of treatment used, it exerted a striking suppressive effect on the pathogenic proclivities of human tubercle bacilli. In a second series, this group,³ using somewhat larger doses, obtained re-

sults that were more striking, and it was shown that there was a reversal from positive to negative tuberculin sensitivity in more than a third of the successfully treated guinea pigs. These early results were considered to be at least comparable with those that they had previously observed with certain sulfones.

Several months after the first report the same workers⁴ made a preliminary report on their first nine months' experience in the treatment of human tuberculosis with streptomycin. The antibiotic was found to exert a limited suppressive effect, especially in some of the more unusual types of pulmonary and extrapulmonary tuberculosis. There was evidence to suggest a temporary inhibition of the multiplication of the organisms, but no rapidly effective bactericidal action could be demonstrated.

In another series of studies with streptomycin in guinea pigs, Smith and McClosky⁵ were able to show that the chemotherapeutic effect of streptomycin in less than one twentieth of the maximum tolerated dose was superior to that obtained with oral doses of Promin up to about half the maximum that these animals could tolerate. With a suitable combination of streptomycin and Promin they obtained results superior to any that they had previously observed. Others later found that streptomycin combined with Diasone, another sulfone related to Promin, exerted a synergistic or additive therapeutic effect in the treatment of experimental tuberculosis in guinea pigs.⁶ A similar superiority of combined therapy was demonstrated in experimental infections in rats.⁷

At about that time Youmans and McCarter⁸ showed that streptomycin exerts a marked suppressive effect in experimental pulmonary tuberculosis of white mice. Youmans⁹ also tested five highly virulent strains in vitro and found the lowest bacteriostatic concentration to be between approximately 0.1 and 0.8 units per cubic centimeter, but more than 50 units per cubic centimeter were required to exert a bactericidal action on 0.1 mg of these organisms.

It was soon demonstrated, however, that tubercle bacilli readily acquire resistance to streptomycin during treatment.¹⁰ Tubercle bacilli isolated from 8 of 12 patients after treatment showed marked resistance, in seven of these eight strains, the re-

istance had increased five hundred to a thousand times when compared with that of the strains isolated from the patients before treatment. These resistant strains were found to be as virulent for white mice as the original streptomycin-sensitive strains, and such infections were not suppressed by streptomycin.¹¹

The most extensive clinical trials that have been reported to date are those of Hinshaw and his associates.¹² The results that they noted in some types of cases were highly encouraging, but certain limitations of therapy also became evident.

Their first 100 patients included 12 with miliary tuberculosis, 9 of whom presented clinical evidence of meningitis. Only 4 of the latter survived, the periods ranging from two to ten months, and they were the only patients in the group to receive intrathecal as well as intramuscular injections of streptomycin. The cerebrospinal fluid returned to normal in only 2 of these cases. One patient who received a six-month course of treatment flared up after an interval of a month, indicating that infection may persist in spite of striking clinical improvement. More significant is the fact that all 4 survivors were left with severe neurologic damage.

Some evidence of improvement was also noted in cases of severe moderately advanced or advanced cases of active and progressive nonsurgical pulmonary tuberculosis. After treatment for two to six months definite roentgenographic improvement was observed in 25 of 32 such cases. In 12 patients there was evidence that pulmonary cavities had closed, but in 6 others thick-walled cavities persisted despite the treatment. Tubercle bacilli disappeared from the sputums of 13 patients, but in 15 others they persisted despite prolonged therapy. There was no demonstrable progression of the lesions in any of the cases. All those that were un-

improved had advanced lesions with thick-walled cavities of long standing. In 6 patients reactivation attended the discontinuance of treatment, but 2 of them promptly improved again when the treatment was reinstituted. Five of the patients had died at the time of the report, 1 of them had had a reactivation four months after a course of treatment carried out over a six-month period and failed to respond to

another course because the infecting organisms had become resistant.

Ulcerating tuberculous lesions of the respiratory tract, including the larynx, hypopharynx, trachea and larger bronchi, seem to have responded favorably in many cases. Tuberculous empyema, on the other hand, failed to improve following intrapleural injections alone in 4 cases, and only 1 of 3 others showed any improvement from

combined intrapleural and intramuscular treatment. In tuberculosis of the genitourinary tract the streptomycin appeared to have only a palliative action and was not considered to be a substitute for surgical measures when indicated.

The dosage that Hinshaw and his associates recommend in adults is from 1 to 3 gm daily in four or six intramuscular doses. They prefer sterile water as a diluent and use concentrations of 100 to 250 mg of streptomycin per cubic centimeter. For intrabronchial use or as an aerosol they advise concentrations of 25 to 100 mg per cubic centimeter, and for intrathecal injections they suggest 100 to 200 mg in 1 to 5 cc of cerebrospinal fluid or of physiologic saline solution every twenty-four to forty-eight hours. Prolonged treatment for at least two to four months is required. Untoward reactions, including fever, rashes and otic complications,^{13, 14} must be expected. They suggest that further treatment should be denied any patient in whom such complications arise and in whom the prognosis by conventional methods of therapy is good. They believe, however, that these reactions

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are usually sufficiently mild to be disregarded in the progressive types of tuberculosis that are not amenable to other therapy. Most important, however, they emphasize that streptomycin is not to be regarded as a substitute for other and proved effective forms of treatment of tuberculosis.

Some preliminary observations by McDermott were summarized in the report of the National Research Council.¹⁵ His results also suggested that streptomycin exerts a definite action on the tuberculous process. This effect was most striking in hematogenous lesions. It was also noticeable in the exudative and moderate advanced type of tuberculosis but was less striking in cases with caseous lesions. Effects on central-nervous-system infections were impressive but not sustained. His more recent results are awaited with considerable interest.

Direct reports from the rather extensive program under way in the hospitals of the Veterans Administration are not yet published. A press release,¹⁶ however, indicates that the early results were favorable enough so that the program was extended to nineteen study units. About three fourths of the patients with pulmonary tuberculosis seem to have shown some improvement. The long-range effects are not yet known, and the incidence of relapses and of the development of resistant strains in this and other groups of cases will be helpful factors in determining the broader usefulness of streptomycin in pulmonary tuberculosis.

In the meantime variable results have been reported in isolated cases or small groups of cases of tuberculous meningitis in addition to those already mentioned. There was recovery, with apparent improvement in the neurologic findings, among 3 of 9 such cases.¹⁷⁻¹⁹ The use of streptomycin for prolonged periods seems indicated for cases of tuberculous meningitis and may be expected to yield some favorable results provided that treatment is given intrathecally and intramuscularly and that there are no coexisting caseous pulmonary or extensive intracerebral lesions.

From the point of the community as a whole, it is probably wise at present to limit the use of streptomycin entirely to the few clinics where carefully controlled and prolonged treatment and study are

possible. Only on the basis of the results in such controlled groups of cases may one expect to determine the real and permanent value of streptomycin in the various forms of tuberculosis and to recommend a nation-wide program for its use in individual cases and in groups of cases. General hospitals are not at present equipped to handle this problem and should not be expected to do so, and it is still too soon even to recommend a long-range program for specialized institutions. In the meantime it is hoped that more effective, less expensive and less toxic agents will become available, particularly ones with which the development of bacterial resistance is not such a prominent feature.

REFERENCES

1. Schatz, A., Bugie, E., and Wakeman, S. A. Streptomycin, substance exhibiting antibiotic activity against gram positive and gram negative bacteria. *Proc Soc Exper Biol & Med* 55:669, 1944.
2. Feldman, W. H., and Hinshaw, H. C. Effects of streptomycin in experimental tuberculosis in guinea pigs: preliminary report. *Proc Staff Meet, Mayo Clin* 19:593-599, 1944.
3. Feldman, W. H., Hinshaw, H. C., and Mann, F. C. Streptomycin in experimental tuberculosis. *Am Rev Tuberc* 52:269-298, 1945.
4. Hinshaw, H. C., and Feldman, W. H. Streptomycin in treatment of clinical tuberculosis: preliminary report. *Proc Staff Meet Mayo Clin* 20:313-318, 1945.
5. Smith, M. I., and McClosky, W. T. Chemotherapeutic action of streptomycin and promin in experimental tuberculosis. *Public Health Rep* 60:1129-1138, 1945.
6. Callomon, F. T., Kolmer, J. A., Rule, A. M., and Paul, A. J. Streptomycin and diaseone in treatment of experimental tuberculosis in guinea pigs. *Proc Soc Exper Biol & Med* 63:237-240, 1946.
7. Smith, M. I., McClosky, W. T., and Ensmart, E. W. Influence of streptomycin and promin on proliferation of tubercle bacilli in tissues of albino rat. *Proc Soc Exper Biol & Med* 62:157-166, 1946.
8. Youmans, G. P., and McCarter, J. C. Preliminary note on effect of streptomycin on experimental tuberculosis of white mice. *Quart Bull Northwestern Univ Med School* 19:210, 1945.
9. Youmans, G. P. Effect of streptomycin *in vitro* on *M. tuberculosis var. hominis*. *Quart Bull, Northwestern Univ Med School* 19:207-209, 1945.
10. Youmans, G. P., Williston, E. H., Feldman, W. H., and Hinshaw, H. C. Increase in resistance of tubercle bacilli to streptomycin: preliminary report. *Proc Staff Meet, Mayo Clin* 21:126, 1946.
11. Youmans, G. P., and Williston, E. H. Effect of streptomycin on experimental infections produced in mice with streptomycin resistant strains of *M. tuberculosis var. hominis*. *Proc Soc Exper Biol & Med* 63:131-134, 1946.
12. Hinshaw, H. C., Feldman, W. H., and Pfuetze, K. H. Treatment of tuberculosis with streptomycin: summary of observations on one hundred cases. *J A M A* 132:778-782, 1946.
13. Brown, H. A., and Hinshaw, H. C. Toxic reaction of streptomycin on eighth nerve apparatus. *Proc Staff Meet Mayo Clin* 21:343-352, 1946.
14. Fowler, E. P., Jr., and Seligman, E. Otic complications of streptomycin therapy: preliminary report. *J A M A* 133:87-91, 1947.
15. Committee on Chemotherapeutics and Other Agents, National Research Council. Streptomycin in treatment of infections: report of one thousand cases. *J A M A* 132:4-11 and 70-77, 1946.
16. Washington Letter. President asks continuance of controls on streptomycin. *J A M A* 133:482, 1947.
17. Cooke, R. E., Dunphy, D. L., and Blake, F. G. Streptomycin in tuberculous meningitis: report of its use in one-year-old infant. *Yale J Biol & Med* 18:221-226, 1946.
18. Krafchik, L. L. Tuberculous meningitis treated with streptomycin. *J A M A* 132:375, 1946.
19. DeBakey, M. E., and Pulaski, E. J. Analysis of experience with streptomycin therapy in United States Army hospitals: preliminary report. *Surgery* 20:749-760, 1946.

SURGICAL TRAINING

CERTAIN aspects of the future of postgraduate surgical training are brought out in a letter published elsewhere in this issue of the *Journal*. The problem is only another one of those that have been raised by a rapidly changing socioeconomic order and that have recently called forth many letters and editorials in medical periodicals. Adequate medical and nursing care, a sufficient number of hospital beds and efficient graduate training of all types have received consideration but it is often difficult to decide which is the cart and which is the horse.

The correspondent points out that the so-called "ward beds" in the teaching hospitals are for various reasons, becoming fewer and fewer and that the opportunities for the proper surgical training of interns and residents are consequently becoming poorer and poorer.

There is no doubt that the numbers of ward beds are lessening, and this will undoubtedly continue as various types of insurance covering hospital and medical care increase in popularity. The situation is further complicated by the fact that ward-plan subscribers to the Blue Cross who are also subscribers to the Blue Shield should rightfully be operated on by a participating surgeon rather than by a member of the house staff. Although it is acknowledged that in the interest of surgical training, by far the majority of ward patients in the large teaching hospital should be operated on by members of the resident staff, it is obvious that this is becoming increasingly difficult.

Another problem concerns the young surgeons who have completed their residencies and who unfortunately for themselves and for the communities in which they are needed, elect to remain in the large teaching hospitals. In such institutions these men are on service for periods of several months during the year, but if they are fair to the resident staff, "handing down" the bulk of the operative work, they get little return in practical experience from the amount of time that they devote to the hospital. On the other hand, the young surgeon who has had four or five years of active well supervised training fares little better if he goes to a com-

munity hospital unless he is fortunate or wise enough to choose a locality in which there is real need for a surgeon. As a rule his operative surgery is limited to what comes his way in private practice.

These trends appear to be inevitable and it seems obvious that the present system of postgraduate surgical training will not suffice and that it has a tendency to disrupt an equitable distribution of surgeons. Too few opportunities are available for postgraduate training furthermore too many well trained young surgeons remain in the large teaching centers partly because little incentive is offered for moving to smaller communities. Three possibilities as a means of relieving the situation are available — more widespread adoption of the fellowship or preceptorship as a method of surgical training, the development of community hospitals as teaching centers and subsidization of the young surgeon who locates in a small community. Other schemes will undoubtedly be devised as the necessity arises. Certainly efforts should be made to meet the demand not only for an increasing number of well trained surgeons but also for their equitable distribution throughout the country.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

CRABTREE — E. Granville Crabtree, M.D. of Brookline died May 30. He was in his sixty-fourth year.

Dr. Crabtree received his degree from Harvard Medical School in 1914. He was urologist at the New England Baptist and Beth Israel hospitals and consulting urologist at the Newton-Wellesley Hospital. He was a former president of the New England Urological Association and was president-elect of the American Urological Association. He was a member of the American Association of Genito-Urinary Surgeons, New England Obstetrical and Gynecological Society and New England Surgical Society and a fellow of the American College of Surgeons and American Medical Association.

His widow, a daughter and two sons survive.

GARFIELD — Walter T. Garfield, M.D. of Belmont, died May 31. He was in his sixty-sixth year.

Dr. Garfield received his degree from Harvard Medical School in 1909. He was emeritus professor of dermatology at Tufts College Medical School and was a member of the staff of the Boston City Hospital. He was chief of the Outpatient Clinic, Cambridge City Hospital and consulting physician at the Norwood and Long Island hospitals. He was a member of the American Academy of Dermatology and Syphilology and a fellow of the American Medical Association.

His widow, two sons, a sister and three brothers survive.

MUSSO — George H. Musso, M.D. of Lynn died March 1. He was in his seventy-third year.

Dr. Musso received his degree from New York University Medical College in 1898. He was administrator of the Union Hospital, Lynn.

CORRESPONDENCE

THE FUTURE OF POSTGRADUATE TRAINING IN SURGERY

To the Editor It must be apparent to all concerned with postgraduate surgical training that serious threats are arising to endanger the system as it exists today. Perhaps this system is not a desirable one, but its products have certainly brought an enviable reputation to American surgery throughout the world. Whereas gradual changes for the better should be a natural process of evolution in any system, it is envisaged that future changes for the worse are in store for this particular branch of postgraduate training.

The components that make up a well balanced surgical training program should give a man the opportunity to become familiar with the various preoperative and postoperative measures that are the most acceptable for any particular situation that may arise. He should have the opportunity to enter investigative work and to attend clinics and teaching sessions that are ably directed and designed to inculcate the principles of surgical anatomy, physiology and pathology. A pupil under such a well balanced program should become adept in handling patients and should become familiar with and able to execute various technics and maneuvers concerned with diagnosis and treatment.

One feature deserves special emphasis, since it should constitute a part of every program designed to produce a well trained surgeon. It is the *sine qua non* and at the same time the *bête noire* of all those seeking surgical training today. It is a feature with which training programs in medicine and its various specialties are not confronted to such a serious degree. This is the opportunity for a man to do various surgical procedures *himself*, under proper guidance. If this opportunity is lacking, failure is a certainty, no matter how well thought out and directed all other parts of the program may be.

This feature of surgical training aids both the surgeon and the patient. It benefits the surgeon in giving him a well rounded training, confidence in himself, coolness under trying situations and that intangible something called "judgment," which is the product only of experience. It benefits the patient by giving him expert surgical attention at a low cost. A young surgeon in training, with a good fundamental background, operating daily on major cases, will probably perform more ably in the average operation than the older surgeon who operates on the occasional patient in private practice. The former is subjected to closer scrutiny and to greater criticism, and this offers considerable stimulus to the average conscientious intern or resident.

Great upheavals in the social system of the world, and of this country in particular, are in progress. One of these is concerned with the redistribution of the wealth. One hears, and reads in various journals and newspapers, of socialized medicine, the Wagner-Murray-Dingell Bill and various insurance plans designed to raise the standard of medical care. The attempt of organized medicine to keep bureaucracy, political pilfering and graft from its doorstep is the natural reactionary development to many of these proposals.

It is quite doubtful that anyone could marshal an effective argument against the general ideas embodied by the Blue Cross today. Unquestionably, a great need was fulfilled by the development of this plan. What it may lead to, however, is another thing. Certainly, no business should be allowed the power to dictate policies that are not in the best interests of the medical profession.

There has been a noticeable trend in recent years of an increasing demand for private beds and a coincidental lessening of the demand for ward care. This is due to many factors, such as an increased national income, changes in the distribution of income and the growth of insurance plans. Some institutions have been forced to close off varying numbers of ward beds owing to a shortage of nurses, which is related in part to some of the aforementioned factors. Increased operational costs for hospitals have almost doubled the rates for ward care. The clamor for more private beds grows louder daily. In fact, at the present time, a plan is even being considered by which private patients would occupy ward beds. It is said that the objective of certain advocates of socialized medicine is to have multiple group practices, which would be financed by the state, with the assistance of federal grants. All patients under the care of such groups would be on a private or semi private status.

The term "ward beds" is used in reference to beds occupied by patients in a teaching institution under the care of the house and visiting staffs. No professional fees are paid by these patients. These beds are not necessarily free, although in some instances they are. If these beds are to be occupied more and more by private patients and those benefiting from employer's insurance, Blue Cross and the like, what beds are to be employed for teaching purposes? A possible answer is the fellowship system, which is used in various clinics throughout the country. This has a definite and highly useful place in graduate surgical training. The time for this type of training, however, is after a certain amount of fundamental and operative experience has been obtained, so that the various diagnostic and therapeutic technics executed by the highly trained surgeons in these great centers can be appreciated. It has been said that no matter how long one watches a great artist playing the piano, one can gain proficiency only by long hours of practice. The combination of watching and doing is the ideal one.

As the ward beds are encroached on by private cases, the will be fewer and fewer cases under the care of the house staff. Coincidentally, more and more men desire long training, stimulated by the requirements of the American College of Surgeons and American Board of Surgery. Thus the problem of adequate training for the young surgeon becomes increasingly difficult. No one will deny that increased training is a desirable thing, but where are the beds to train so many for so long? That would be difficult to answer in an event, but with the increasing shortage of ward beds it will become even more so.

The answer to these questions must be forthcoming soon. There are answers. The questions are not insoluble.

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BOOK REVIEWS

Peptic Ulcer. Its diagnosis and treatment. By I. W. Helk, M.D., and A. Allen Goldbloom, M.D. 8°, cloth, 383 pp with 110 illustrations. Springfield, Illinois: Charles C. Thomas, 1946. \$6.50.

This monograph is unusual chiefly because it has been put together by two broadly trained internists who do not claim to be gastroenterologists. It presents a pleasant and easily readable account of peptic ulcer and its vagaries.

The general architecture of the book is along modern lines. The first chapter deals with the pathogenesis of ulcer, the second with pathology, the third with symptoms, and so on down to a discussion of the complicated ulcer and the indications for surgery—without mention, incidentally, of vagotomy.

The authors have been industrious, at the end of each chapter is a list of reliable bibliographic references, the illustrations are well chosen, and their literary style is plain and simple. Captain Herman Schildkrout—another internist without professed gastroenterologic leanings—has supplied a chapter entitled "Dyspeptic Soldier," which discusses functional indigestion with a fair degree of adequacy.

On the whole, the volume is simple and unpretentious. It makes no claim to educate the highly specialized specialist. Yet it is likely to prove a comfortable vehicle of information to the readers for whom it was written—the busy physician in general practice and the medical student who is preparing for tomorrow.

Lippincott's Quick Reference Book for Medicine and Surgery. A clinical, diagnostic, and therapeutic digest of general medicine, surgery and the specialties, compiled systematically from modern literature. By George E. Rehberger, M.D. Thirteenth edition. 4°, cloth, 1461 pp, with 302 illustrations. Philadelphia: J. B. Lippincott Company, 1946. \$15.00.

This popular, standard reference book, first published in 1920, has been thoroughly revised for this thirteenth edition. The sections on obstetrics, skin, eye, ear, nose and throat have been rewritten. Emphasis is placed on the clinical aspects of medicine. Part eleven consists of a large valuable alphabetical list of drugs with their dosage, solubility, method of administration, physiologic and toxic action and therapeutic indications. There is also a pharmacologic index arranged by classes of drugs, as well as a comprehensive

index of subjects. The volume is well adapted for quick reference and is suitable for public libraries. It is well printed in two columns, with a good type on good paper, and is substantially bound.

Practical Malariaology. Prepared under the auspices of the Division of Medical Sciences, National Research Council, by Paul F. Russell, M.D., M.P.H., Luther S. West, Ph.D., and Reginald D. Manwell, Sc.D. 8°, cloth, 683 pp., with 238 illustrations. Philadelphia: W. B. Saunders Company, 1946. \$4.00.

Raymond B. Fosdick, of the Rockefeller Foundation, in the foreword of this volume, describes malaria as "a stubborn disease, slow to kill, quick to incapacitate and hard to cure." This book is a balanced and authoritative study presenting the varied and complex problems of malariaology and setting forth the newer knowledge about this widespread disease. The experience and judgment of the authors are reflected in the thorough and competent treatment of every phase of the subject. Dr. Russell has devoted approximately twenty years to the study of this disease in numerous highly malarious areas of the world.

The clinician will find a concise description of the disease and the newer dosage schedules for prophylaxis and treatment that were developed during World War II. The new antimalarial drugs, chloroquine and paludrine, are also mentioned, along with the information available about results and usefulness at the time the book went to press. A short chapter on therapeutic malaria in the treatment of general paresis is given.

Since the specific diagnosis of this disease depends on the demonstration of parasites in the blood, the laboratory technician will appreciate the thorough descriptions of human and also animal species of plasmodia. Excellent colored plates of stained human malarial parasites in both thick and thin films are included. Technical methods for staining, preserving and culturing parasites are given, and procedures for handling, rearing and identifying mosquitoes are presented in detail.

After reading the thorough sections on epidemiology and control of the disease and its anopheline vectors, the reader will have no illusions about the simplicity of malariaology. Nevertheless, the community and technical problems of malaria control, the methods of attack and the results to be expected from control measures are applicable to a wide variety of malarial situations. The methods given for mosquito control and for drainage and filling of breeding places will be useful to public-health officers and sanitary engineers who are responsible for the general control of mosquitoes as pests, as well as for their eradication as vectors of malaria in endemic areas.

This volume is what the title indicates—a practical manual for use in the clinic, in the laboratory and in the field for the diagnosis, prophylaxis, treatment, control and study of malaria.

Handbook of Neurological Examination and Case Recording. By D. Denny-Brown, M.D. 12°, paper, 112 pp. Cambridge: Harvard University Press, 1946. \$1.75.

This brief manual is useful for house officers and students in a neurologic clinic. Since many manuals of a similar nature are available, it seems hardly necessary to add a new one. All the material contained in it is readily available in standard textbooks on neurology, where it should be. Although this book is sound, the need for it appears to be slight.

Operative Gynecology. By Richard W. TeLinde, M.D. 8°, cloth, 751 pp., with 309 illustrations and 9 color plates. Philadelphia: J. B. Lippincott Company, 1946. \$18.00.

This admirable textbook of operative gynecology is wholly in the best Hopkins tradition and derives lineally from the pioneer work of Howard Kelly. In a series of thirty-eight chapters, the author describes succinctly and with utmost clearness all the classic gynecologic procedures and a large number of new operative techniques, most of which he has himself devised. Each chapter is followed by a brief but expertly selected bibliography of references to the literature. The work is copiously illustrated with original drawings in black and white and fifteen subjects in full color on nine plates. The merit of the text is matched by that of the

illustrations, the majority of which are by James Didusch and the late Max Brödel. From every standpoint this is an exceptional book, which may be unhesitatingly pronounced the finest of its class to date.

Their Mothers' Sons. By Edward A. Strecker, M.D., Sc.D., Litt.D., LL.D. 8°, cloth, 220 pp. Philadelphia: J. B. Lippincott Company, 1946. \$2.75.

Some of the major issues with which psychiatrists concern themselves in their practice and study continue to be as baffling now as they were when man first surveyed man with the aim of improving his social condition and personal welfare. But much knowledge is being accumulated, and many wise persons are drawing their own conclusions about the material with which they work in this field.

One of these is Dr. Edward A. Strecker, who has spent the greater part of his life treating maladjusted patients and studying their problems. He has synthesized one of the results from this lifetime of labor into a simple formula that anyone can understand. It is the three letter word "Mom," first emphasized by Mr. Philip Wylie, but now given by Dr. Strecker the full stature and strength required to make it a living concept. Alfred Adler is reported to have said, "Children are the victims of their incessant mothers and their infrequent fathers." Perhaps this explains why Dr. Strecker fixes the blame on Mom instead of Pop. At any rate, the result of her sins of commission is the same as his sins of omission—an inadequate or maladjusted person who cannot work or fight and who seems incapable of learning to be a happy and useful citizen.

If anyone is an authority on this subject it is Dr. Strecker. He has practiced psychiatry in Philadelphia for years. He has dealt as a consultant with psychiatric problems in the Army and Navy. In the course of his work Dr. Strecker has made prolonged and minute investigations of countless cases. In all this, he has been profoundly impressed by the relationship of the mother and child and its effect on the child's performance and accomplishments later in life. Starting with an absolutely open mind or perhaps with an inclination to favor the interests and influence of the mother, Dr. Strecker concludes that at least one type of neurotic life pattern is due more to her than to anybody else. After reaching this conclusion, he devotes a great part of this extraordinary book to a description of what a Mom is and is not and to a detailed analysis of what such mothers do to their children and how they do it. This book is a self-administering text, by means of which any woman who suspects herself of being a Mom can soon find out the awful truth one way or the other. Dr. Strecker even goes farther and gives the reader some indication of what to do about it. For once and for all, Dr. Strecker presents a new and dynamic concept that is already proving useful in home and school where the danger of Momism is greatest.

This book will also be helpful to the physician who has a Mom to deal with. At least it will provide information in terms of Dr. Strecker's analysis. One question that comes up is, "What is a Mom?" The answer, according to this book is, "Mom is a mixed up mother who mixes up her child." This mix-up can occur anywhere along the line, but it may occur early and is usually maintained throughout the years when the child is in closest touch with the mother and most receptive to the impression of unfavorable as well as favorable features of her personality. Some would call it a vitriolic book. Perhaps it is. It is a book that may jolt some mothers into seeing themselves as others see them—particularly psychiatrists. But it is certainly not a book to give as a present on Mother's Day. Dr. Strecker should write a companion volume on Pop.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Tutoring as Therapy. By Grace Arthur. Ph.D. 8°, cloth, 125 pp. New York: Commonwealth Fund, 1946. \$1.50.

Parenteral Alimentations in Surgery With special reference to proteins and amino acids By Robert Elman, M D, associate professor of clinical surgery, Washington University School of Medicine 8°, cloth, 284 pp, with 31 figures and 21 tables New York Paul B Hoeber, Incorporated, 1946 \$4 50

Devil by the Tail By Langston Moffett 8°, cloth, 431 pp Philadelphia J B Lippincott Company, 1947 \$3 00

Manual of Diagnostic Psychological Testing Volume II Diagnostic Testing of Personality and Ideational Content By David Rapaport, Ph D, and Roy Schafer, BS With the collaboration of Merton Gill, M D 8°, paper, 100 pp, with 12 illustrations and 5 tables New York Josiah Macy Foundation, 1946

Cardiovascular Diseases By David Scherf, M D, associate professor of medicine, New York Medical College, Flower and Fifth Avenue Hospitals, and Linn J Boyd, M D, professor of medicine, New York Medical College, Flower and Fifth Avenue Hospitals 4°, cloth, 478 pp, with 56 illustrations Philadelphia J B Lippincott Company, 1946 \$10 00

Your Rheumatism and Backaches By Joseph D Wasseraug, M D 8°, cloth, 254 pp New York Wilfred Funk, Incorporated, 1947 \$2 50

Scientists Against Time By James Phinney Baxter, 3rd 8°, cloth, 473 pp, with 74 illustrations Boston Little, Brown and Company, 1946 \$5 00

The American Hospital By E H L Corwin, Ph D 8°, cloth, 226 pp New York The Commonwealth Fund, 1946 \$1 50 Studies of the New York Academy of Medicine, Committee on Medicine and the Changing Order

The Centennial of Surgical Anesthesia An annotated catalogue of books and pamphlets bearing on the early history of surgical anesthesia Exhibited at the Yale Medical Library, October, 1946 Compiled by John F Fulton, M D, and Madeline E Stanton, A B 8°, paper, 102 pp, with 8 facsimiles and one portrait New York Henry Schuman, 1946 \$4 00

Victory Over Pain A history of anesthesia By Victor Robinson, M D 8°, cloth, 338 pp, with 17 illustrations and 30 plates New York Henry Schuman, 1946 \$3 50

White Caps The story of nursing By Victor Robinson, M D 8°, cloth, 425 pp, with 24 illustrations Philadelphia J B Lippincott Company, 1946 \$3 75

Health Insurance in the United States By Nathan Sinai, Dr P H, Odin W Anderson, and Melvin L Dollar, School of Public Health, University of Michigan 8°, cloth, 115 pp New York The Commonwealth Fund, 1946 \$1 50 Studies of the Committee on Medicine and the Changing Order of the New York Academy of Medicine

The Second Forty Years By Edward J Steigltz, M S, M D With a foreword by Anton J Carlson, A M, Ph D, LL D, M D, Sc D 8°, cloth, 317 pp, with 18 figures Philadelphia J B Lippincott Company, 1946 \$2 95

Techniques and Procedures of Anesthesia By John Adriani, M D, director, Department of Anesthesia, Charity Hospital of Louisiana, and clinical assistant professor of surgery (anesthesiology), Louisiana State University 8°, cloth, 404 pp, with 123 illustrations Springfield, Illinois Charles C Thomas, 1947 \$6 00

Therapeutic Exercise By F H Ewerhardt, M D, assistant professor of physical medicine, Washington University School of Medicine and Barnes Hospital, St Louis, and Gertrude F Riddle, B S, R N, R P T, instructor, School of Physical Medicine, St Louis University School of Nursing 8°, cloth, 152 pp Philadelphia Lea and Febiger, 1947 \$2 50

Whither Medicine From dogma to science? By Antony Fidler, M D, docent (associate professor) of medicine, University of Warsaw, and senior lecturer in medicine, Polish School of Medicine, Edinburgh 12°, cloth, 115 pp Edinburgh Thomas Nelson and Sons, Limited, 1946 6 sh

Aphasia A guide to retraining By Captain Louis Granich Medical Administration Corps, A U S With an appendix in collaboration with Sergeant George W Pangle, Medical Department, A U S 8°, cloth, 108 pp New York Grune and Stratton, 1947 \$2 75

The Journals and Letters of the Little Locksmith By Arine Butler Hathaway 8°, cloth, 395 pp, with 17 illustrations by the author New York Coward-McCann Corporation, 1946 \$3 75

Medicine in the Changing Order Report of the New Academy of Medicine Committee on Medicine and the Changing Order 8°, cloth, 240 pp New York The Commonwealth Fund, 1947 \$2 00

Fundamentals of Clinical Neurology By H Houston M M D, professor of clinical neurology, Columbia University College of Physicians and Surgeons, and chief, Division of Neuropsychiatry, Montefiore Hospital, Fred A M Ph D, associate professor of anatomy, Columbia University College of Physicians and Surgeons, and Tracy J Putnam, M D, professor of neurology and neurology, Columbia University College of Physicians and Surgeons 8°, cloth, 289 pp, with 96 illustrations Philadelphia Blakiston Company, 1947 \$6 00

A Handbook of Commonly Used Drugs Including measures for the control of diseases peculiar to the tropics and the western hemisphere By Michael Pijoan, M D, director, Chemical Foundation Laboratory, University of Colorado, and Clark Harvey Yeager, M D, Dr P H, chief of medical section, health and sanitation division, Office of Inter-American Affairs, Washington, and lecturer on tropical diseases, Johns Hopkins Medical School and University of Maryland School of Medicine 8°, cloth, 198 pp Springfield, Illinois Charles C Thomas, 1947 \$3 75

Health Reform in New Zealand By Douglas Robb, M Ch M, F R C S (Eng), F R A C S 12°, paper, 104 pp Auckland Whitcombe and Tombs, Limited, 1947

Uterotubal Insufflation A clinical diagnostic method of determining the tubal factor in sterility including therapeutic and comparative notes on hysterosalpingography By J Rubin, M D, clinical professor of gynecology, Columbia University College of Physicians and Surgeons, consultant gynecologist, Mount Sinai Hospital, visiting gynecologist, Montefiore Hospital, and consulting gynecologist, Israel Hospital, New York City 4°, cloth, 453 pp, 159 illustrations, 1 plate and 34 tables St Louis C Mosby Company, 1947 \$10 00

Die hormonalen Aspekte des Fortpflanzungsprozesses Jules Samuels, Chirurg-Frauenarzt, Spezialarzt für endokrinotherapie 8°, cloth, 152 pp Amsterdam Hoeber and Co, N V, 1946

Die Hormonversorgung des Fetus By Jules Samuels, M Chirurg-Frauenarzt, Spezialarzt für endogene Endokrinotherapie. 8°, cloth, 319 pp, with 3 plates Leiden Brill, 1947

Experiences with Folic Acid By Tom D Spies, M D, associate professor of medicine, University of Cincinnati School of Medicine, and director, Nutrition Clinic, Hill Hospital, Birmingham, Alabama 8°, cloth, 110 pp, 34 illustrations and four colored plates Chicago Book Publishers, Incorporated, 1947 \$3 75

The New England Journal of Medicine

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Volume 236

JUNE 26, 1947

Number 26

THE SURGICAL TREATMENT OF URINARY INCONTINENCE*

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BOSTON

THE subject of exertional incontinence in women—or “stress incontinence,” as it is frequently called—has stimulated the imagination of the medical profession for many years. Numerous operative procedures have been devised for the cure of this condition, but as yet no entirely satisfactory technic is available.

This study was stimulated by the work of Dr. William T. Kennedy,¹⁻³ of New York. His results were so far superior to those previously attained that they could not fail to arouse interest.

Up to the time this study was undertaken, the usual procedure employed at the Massachusetts General Hospital for the correction of exertional urinary incontinence was by means of a repair of the anterior vaginal wall and a figure-of-eight or mattress stitch placed at the bladder neck, after the method advocated by Kelly⁴ in 1914. Discarding the untraced cases, Kelly's report showed 41 per cent cures. Our experience with this method gives essentially similar results. Cure may be expected in about half the patients on whom it is used. This is far from satisfactory, and in the uncured group the result is most disappointing to both patient and surgeon.

MECHANISM OF URINARY CONTROL

Much work has been done to determine the exact mechanism of urinary control in women. Careful and detailed anatomic study has been devoted to this subject, and excellent presentations by Kennedy,^{2, 3} Davies⁵ and Curtis^{6, 7} have appeared in recent years. From this mass of detailed work, certain fundamental facts appear that may be used as a basis for an understanding of the problem of urinary incontinence.

The wall of the urethra contains involuntary muscle fibers that become more numerous in the region of the bladder neck, where they are arranged in a circular manner and form what is called the in-

ternal sphincter. This mechanism is under autonomic control and under normal conditions serves to maintain closure of the bladder outlet.

There is also a voluntary sphincter mechanism, which consists chiefly of the sphincter urethrae membranacea. This muscle is contained between the two fascial layers of the urogenital diaphragm, which bridges the anterior portion of the pelvic outlet running from one ischiopubic ramus to the other. The fibers of the sphincter urethrae membranacea arise from the inner surface of the inferior pubic ramus and from the investing fascial layers and encircle the urethra. Posteriorly, they blend with the deep transverse perineal muscle to encircle the vagina. The sphincter urethrae membranacea is innervated by the perineal branch of the pudendal nerve, and its action is to constrict the urethra, making possible the voluntary interruption of the urinary stream.

The anterior fibers of the levator ani arise from the inner surface of the superior ramus of the pubis, and as they run posteriorly to insert into the coccyx, a few fibers are given off to the urethra. The importance of these fibers in contributing to the voluntary sphincter mechanism has been stressed by some authors.

If the mucous membrane is elevated from the anterior vaginal wall and care is exercised to keep the dissection close to the mucosa, an avascular plane is encountered, and a firm fibrous layer is uncovered. This is the pelvic fascia, and as the dissection is carried forward toward the external meatus, the region of the urogenital diaphragm is exposed (Fig. 2).

MECHANISM OF URINARY INCONTINENCE

When a patient with stress incontinence is examined in the lithotomy position, the urethra, instead of pointing almost horizontally, usually assumes a nearly vertical direction. This sagging of the urethra and bladder neck away from the pubic arch, which was emphasized by Watson⁸ in 1924, results from a tearing of the layers of pelvic fascia between the bladder and the anterior vaginal wall.

*Presented at the annual meeting of the New England Surgical Society, Worcester, Massachusetts, October 4, 1946.
†From the Gynecological Service, Massachusetts General Hospital.
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and the structures of the urogenital diaphragm. The displacement of the bladder neck and urethra impairs the function of the sphincter mechanism, leading to stress incontinence.

Whether the functional impairment of the sphincter mechanism is due to actual muscular damage to the sphincter urethrae membranacea or to loss of fixation of the urethra and its descent from a normal

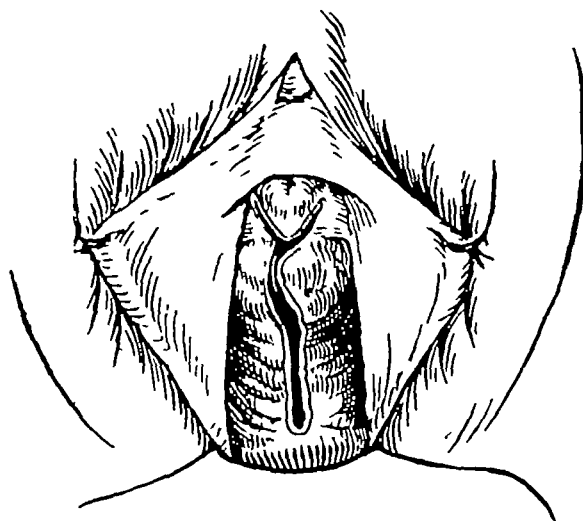


FIGURE 1

An incision has been made in the anterior vaginal wall. The bulging of the anterior vaginal wall proximal to the external meatus is due to the sagging of the urethra and bladder neck.

position behind the pubic arch has not been established.

Under normal conditions the sphincter urethrae membranacea serves to allow voluntary interruption of the urinary stream. Its action is not normally required to prevent the involuntary escape of urine from the bladder even under conditions of stress and increased intravesical pressure. This function is fulfilled by the involuntary sphincter mechanism. It is my belief that stress incontinence occurs when the bladder neck and urethra sag away from their normal positions behind the pubic arch, because this results in a stretching and distortion of the bladder neck and proximal urethra that render ineffective the action of the internal (involuntary) sphincter.

The success of an operative procedure for stress incontinence depends on the replacement of the urethra and bladder neck in their normal positions, by whatever means attained, rather than on the reapproximation of voluntary muscle fibers. The importance of this restoration of normal anatomic relations in providing a good functional result has been emphasized by Kennedy.⁹

METHODS OF REPAIR

A great many surgical procedures have been devised for the cure of exertional urinary incontinence in women. They fall into three general types

The first comprises attempts to reconstruct the existing structures of the urethra or bladder neck, or both, by means of a vaginal plastic procedure. These vary from the simple Kelly⁴ stitch described above, and many modifications thereof, to more elaborate operations, such as that described by Kennedy¹⁻³ and Frost.¹⁰ Kennedy's technic is based on the concept that, in addition to the displacement of the urethra and bladder neck described above, the function of the voluntary sphincter has been impaired by the formation of scar-tissue bands between the urethra and the pubic rami laterally. To correct this, the vaginal mucosa is elevated from the bladder neck and posterior two thirds of the urethra, and the dissection carried laterally under the pubic rami until the urethra is entirely freed of its lateral attachments, including any post-traumatic scar tissue that may be present. The urethra is then plicated in the midline to restore the function of the voluntary sphincter. Kennedy obtained excellent

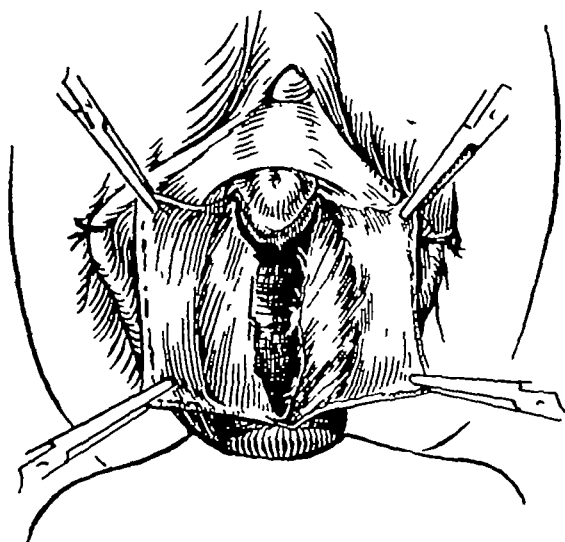


FIGURE 2

The mucous membrane is elevated. In the midline the layers are adherent, and the cleavage plane is indistinct. As the dissection is carried laterally, close to the mucosa, a good avascular plane is encountered, which may be easily followed laterally to the pubic rami. The pelvic fascia is revealed as a smooth glistening layer, and as the dissection is carried anteriorly toward the external meatus, the region of the urogenital diaphragm is exposed.

results by this method, reporting 35 cases with cures in 32.

The second general type of operative repair involves the use of various muscle or fascial transplants. Some of these procedures are done entirely from below, and others, partly vaginally and partly suprapubically. Portions of the levator muscles, the gracilis, the pyramidalis, strips of fascia from the rectus sheath or external oblique and various other

structures have been used. Recently, Price,¹¹ Aldridge,¹² Meigs¹³ and Studdiford^{14, 15} have reported excellent results through the use of a fascial sling

muscle of the trigone in the transvesical repair of the internal sphincter has been stressed by Macky.¹⁶

A nonoperative method for the treatment of stress incontinence was reported by Murless,¹⁷ who employed periurethral injections of a sclerosing solution (5 per cent sodium morrhuate). By this technique he was able to produce cures in 60 per cent of a series of 20 cases.

MATERIAL STUDIED

In the selection of cases for this study, the choice was limited to patients in whom the condition was believed to result from the trauma of childbirth. Patients who were nulliparous or in whom some congenital abnormality was present were not included.

Sixty-three operations for the relief of stress incontinence were done on 62 patients. Of these, 15

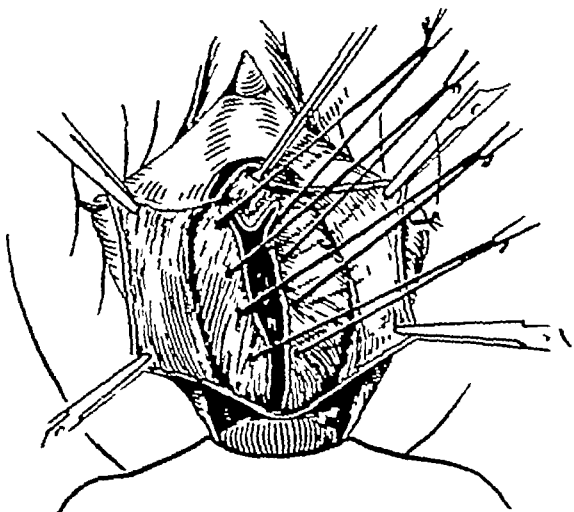


FIGURE 3

The pelvic fascia and urogenital diaphragm are approximated over the urethra and bladder neck.

This method seems to offer a means of replacing the bladder neck in its normal position behind the pubic

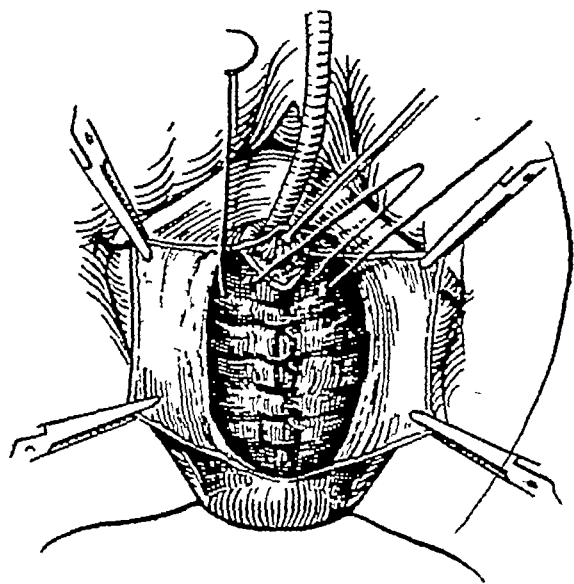


FIGURE 4

The pelvic fascia and urogenital diaphragm are reinforced by a second row of sutures.

arch when such replacement might be impossible to attain otherwise.

The third procedure employs the transvesical approach for the repair of the sphincter mechanism at the bladder neck. The value of recognizing the

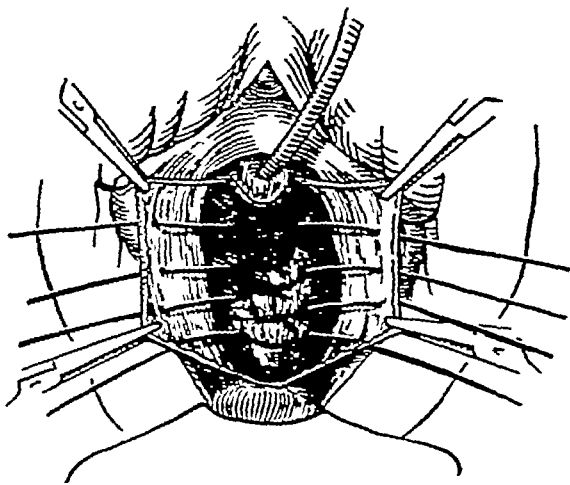


FIGURE 5

Sutures are placed to close the mucous membrane and to anchor it to the underlying fascia. (This anchoring of the mucosa to the fascia has since been omitted.)

had had one or more previous operations for the same condition without success. These operations were done between 1939 and 1942, and it was believed that a follow-up study, after a period of over four years, would be of value. Of the cured patients, 12 could not be traced, and the follow-up period in these cases averaged fourteen months. The remaining 32 cured patients were traced, with an average follow-up interval of seventy months.

OPERATIVE PROCEDURE AND RESULTS

In the first 42 cases the technique described by Kennedy was followed as closely as possible. In this group 29 patients, or 69 per cent, were cured.

The stripping of the lateral attachments of the urethra from the pubic rami was then discontinued for two reasons: the dissection may result in considerable hemorrhage, from damage to the veins

about the bladder neck, which at times is difficult to control, and these lateral structures were considered to be the normal attachments of the pelvic fascia and urogenital diaphragm, so that their loss might interfere with the replacement of the bladder neck and urethra in the normal positions. Thus, in the last 21 cases the procedure resolved itself into the elevation of the vaginal mucosa from the entire urethra and bladder neck and a careful plication of

another case a cystocele occurred following the operation, and a later repair of this was necessary.

Three patients developed urethrovaginal fistulas requiring repair. It is believed that this may have been due to anchoring the mucosa to the underlying layer in the completion of the closure (Fig 5), and this procedure has been abandoned.

SUMMARY

The anatomy of the internal (involuntary) and the external (voluntary) sphincter mechanisms of the bladder and urethra in women are briefly described.

The relative importance of damage to the voluntary and involuntary sphincters in the production of stress incontinence is discussed.

Various operative procedures used for the cure of stress incontinence are briefly described.

Sixty-three operations were performed in 62 patients for exertional urinary incontinence resulting from childbirth trauma. The operation was successful in 44 cases, or 70 per cent.

Stress incontinence is believed to result when the function of the involuntary sphincter mechanism is impaired owing to stretching and distortion of the bladder neck and proximal urethra. This occurs after trauma that allows these structures to sag away from their normal positions behind the pubic arch. The voluntary sphincter may be damaged in the process, but such damage is of little, if any, importance in the production of stress incontinence.

The success of an operation for stress incontinence is considered to depend on the restoration of the bladder neck and urethra to their normal anatomic positions, allowing the involuntary sphincter to resume its normal function.

REFERENCES

- Kennedy, W. T. Incontinence of urine in female: some functional observations of urethra illustrated by roentgenograms. *Am J Obst & Gynec* 33:19-29, 1937.
- Idem. Incontinence of urine in female, urethral sphincter mechanism, damage of function, and restoration of control. *Am J Obst & Gynec* 34:576-589, 1937.
- Idem. Incontinence of urine in female: study of urethral sphincter under hydrostatic pressure with roentgenograms—sphincter mechanism, loss of control, restoration. *New York State J Med* 38:256-261, 1938.
- Kelly, H. A. and Dumm, W. M. Urinary incontinence in women, without manifest injury to bladder: report of cases. *Surg, Gynec & Obst* 18:444-450, 1914.
- Davies, J. W. Urinary stress incontinence: anatomical defect found and rational method for its treatment. *Surg, Gynec & Obst* 67:273-280, 1938.
- Curtis, A. H., Anson, B. J., and McVay, C. B. Anatomic factors in pathogenesis and treatment of urethrocele and cystocele. *J A M A* 111:903-906, 1938.
- Curtis, A. H. *Textbook of Gynecology*. Fifth edition. 755 pp. Philadelphia: W. B. Saunders Co., 1946.
- Watson, B. P. Imperfect urinary control following childbirth, and its surgical treatment. *Brit M J* 2:566-568, 1924.
- Kennedy, W. T. Urinary incontinence relieved by restoration and maintenance of normal position of urethra. *Am J Obst & Gynec* 41:16-28, 1941.
- Frost, I. F. Urinary incontinence, with special reference to certain factors which are necessary in cure of this condition. *Am J Surg* 71:172-180, 1946.
- Price, P. B. Plastic operations for incontinence of urine and feces. *Arch Surg* 26:1043-1053, 1935.
- Aldridge, A. H. Transplantation of fascia for relief of urinary stress incontinence. *Am J Obst & Gynec* 44:398-411, 1942.
- Meigs, J. V. Discussion of Studdiford.¹⁴
- Studdiford, W. E. Transplantation of abdominal fascia for relief of urinary stress incontinence. *Am J Obst & Gynec* 47:764-775, 1944.

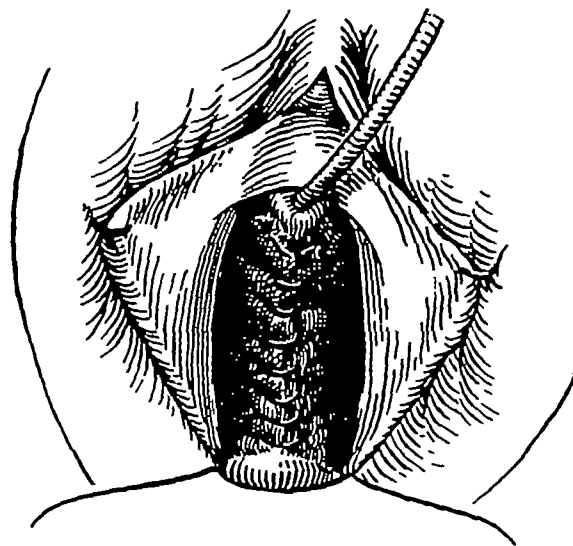


FIGURE 6

The mucous membrane is closed, thus completing the operation.

the pelvic fascia and urogenital diaphragm over these structures. This serves to support the urethra and bladder neck from below and to hold them up behind the pubic arch. The steps of this operation are illustrated in Figures 1 to 6. It is essentially the method advocated by Young¹⁸ in 1922. There were cures in 15 cases, or 71 per cent.

Various types of suture material were used in the repair, including catgut, cotton and silk. Little difference in the results was noted, although catgut seemed to be the best material, perhaps by virtue of a greater inflammatory reaction, with more scar-tissue formation.

A repair of the perineum was carried out in all cases to improve the pelvic support by approximation of the levator ani muscles.

One patient in each of the above groups was changed from being only improved to being cured by the use of periurethral injections of 5 per cent sodium morrhuate. The same treatment on a number of other patients who were not cured gave no improvement.

Complications

One patient developed a perivesical hematoma that became infected and required drainage. In

- 15 Idem. Further experiences in use of transplanted abdominal fascia in relief of stress incontinence *Am J Obst & Gynec* 50 119 137 1945
- 16 Macky F. Operation for cure of stress incontinence in female *J Urol* 52 27-35 1944
- 17 Murliss B. C. Injection treatment of stress incontinence *J Obst & Gynaec Brit Emp* 45 67-73, 1938
- 18 Young E. L. Jr. Urinary incontinence in female *J A M A* 79 1753-1756, 1922

DISCUSSION

DR. EDWARD L. YOUNG (Boston) I should like to emphasize what I believe to be the cause of at least 30 per cent of the failures in this type of operation. These cases must be studied intensively beforehand, because there are many conditions that may make trouble. One is called a "reno-vesicle reflex" — a complicated name for something that is not understood, but it means that because of minor damage to the kidneys there are often bladder symptoms, including incontinence. Infection, which occurs in spite of a perfectly clear urine that is chemically normal, can also cause incontinence.

I believe that some failures are due to the fact that these conditions are not recognized. Last year I had an interesting case of failure. I closed what I was sure was a stress incontinence, and the patient was worse when I got through than before I started. I discovered that urine was draining from the cervix. Further study showed that the patient had had a supravaginal hysterectomy. The surgeon had carefully put a suture through the cervix and the bladder, where there was a valve. When the valve opened the urine poured out through the cervix.

I believe that about every quarter of a century this subject must be studied because it is a bothersome problem to a great many women and the best method is careful dissection, such as that described by Dr. Bartlett, to identify the layer that is a mixture of fascia and muscle tissue. If the cases are selected, I think that the cures will approximate 85 per cent.

DR. STEPHEN RUSHMORE (Boston) I have been interested in this subject for many years, and after operations for this condition I have found so many failures that I hope I have learned something from my experience.

In the first place, a satisfactory test of where the difficulty lies can be made by the use of a Pezzer catheter — not an old one from which the life of the rubber has been boiled out, but a new one that has some rigidity. If such a catheter is introduced and drawn down against the internal meatus of the urethra, the opening of the bladder, it can usually be determined easily that that is the point at which the weakness exists and at which resistance must be built up.

It seems to me that the cause of the failures in many of these cases is the fact that the sphincter muscle — the smooth muscle that is the wall of the bladder and is hypertrophied at this point — is stretched throughout its whole circumference, owing to injury at childbirth. If it is stretched more on the anterior or upper margin, there will be greater difficulty in repair of the organ or the structure so that it will function properly.

If the muscle is stretched at that point, the logical approach seems to be to repair it from above, an impractical method of attack. But that explains I believe, why sewing it up from below in some cases gives such a poor result, because the muscle itself has been weakened at the anterior and upper margin.

I think that the results may be improved by careful plastic operation and placing of sutures — it is the placing of the suture that is of greatest importance — and the testing of the amount of contraction resulting from the operation by the use of the Pezzer catheter.

In some of these cases in elderly women there is the trauma of many childbirths, and the tissue seems to have lost its tone, the muscle itself has lost most of its tone and is extremely flabby. A perfectly satisfactory functional result with a muscle that is practically exhausted cannot be expected in every case.

INFECTION CAUSED BY *STREPTOBACILLUS MONILIFORMIS**

Report of 2 Cases Following Rat Bites

LAWRENCE KILHAM, M D †

BOSTON

INFECTION due to *Streptobacillus moniliformis* is often characterized by fever, a migrating polyarthritides, a skin rash and a relapsing course. A preceding history of rat bite within ten days is frequent. In a few reported cases, however, no source of infection could be established.^{1,2} Place, Sutton and Willner³ described an outbreak occurring in Haverhill, Massachusetts, following the ingestion of raw milk. Organisms isolated from 11 of 13 patients in this epidemic were extensively studied by Parker and Hudson,⁴ who described them as a new species, *Haverhillia multiformis*. Unknown to them at the time, however, Levaditi and his associates¹ had isolated and described the organism a year previously as *Str moniliformis*. The most complete review is that of Brown and Nunemaker.⁵ Watkins⁶ recently summarized 39 cases of rat-bite fever reported in the United States in which *Str moniliformis* was the proved etiologic agent. Positive blood cultures were obtained in the 2 cases described below.

CASE 1. C. J., a 5-month-old infant, was admitted to the hospital on January 29, 1940, after having been severely gnawed by a rat. Physical examination showed a pale infant with a temperature of 102°F, regular respirations and a rapid pulse. There were bites on the right cheek and a large defect in the right wrist, in addition to tooth marks over the right hand.

The right wrist was debrided and irrigated. During treatment pieces of cartilage floated up through the defect. A culture of the wound grew out *Str moniliformis*, as did a blood culture taken on admission. Examination of the blood revealed a red-cell count of 2,220,000, with a hemoglobin of 43 per cent, and a white-cell count of 18,000, with 43 per cent neutrophils, 52 per cent lymphocytes, 4 per cent monocytes and 1 per cent basophils.

The temperature fell to 100°F in 3 days. After a week the temperature alternated between normal and 100°F until discharge. Chlorinate dressings and irrigations were applied to the wound daily, with steady healing and improvement, in spite of an x-ray diagnosis of osteomyelitis in the underlying bones. A blood Hinton test was negative on March 1. On April 28 the patient was sent to a convalescent home.

It is of interest in this case that in spite of extensive rat bites, from which *Str moniliformis* was cultured directly, and an early bacteremia, the disease did not progress to a full picture of rat-bite fever. No skin rash or polyarthritides was noted.

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†Assistant in bacteriology, Harvard Medical School.

CASE 2 P S, a 75-year-old Jewish man, was admitted to the hospital on June 14, 1946, because of fever. A rat had bitten him on the forehead 3 days previously. On the day of admission the patient had fever, chilly sensations, headache, backache and pains in the knees.

Physical examination revealed a well developed and well nourished man lying comfortably in bed. Physical examination was essentially negative except for injection of the conjunctivas and a dry, coated tongue. No skin rash was present. The small wound on the forehead had healed. There was no tenderness, swelling, redness or pain on motion of the joints.

The temperature was 100°F, the pulse 84, the respirations 40, and the blood pressure 120/76. Examination of the blood revealed a hemoglobin of 100 per cent (Sahli) and a white-cell count of 12,300, with 93 per cent neutrophils and 7 per cent lymphocytes. Urinalysis was negative.

The patient was given 40,000 units of penicillin every 3 hours. Within 24 hours he became asymptomatic. The temperature fell to normal within 3 days. Penicillin treatment was continued until June 23, the day of discharge.

On June 20 the white-cell count had fallen to 7900. Blood Hinton tests were negative on July 3 and on July 27.

The blood taken on admission was cultured in a meat-infusion broth*. Within 24 hours there was a fairly abundant growth of *Str. moniliformis*, as determined by the characteristic "fluff ball" appearance of the colonies and the presence of pleomorphic, gram-negative organisms on smear. Identification was further confirmed by agglutination tests. Antiserums previously prepared in rabbits against three strains of *Str. moniliformis*—two from patients with rat-bite fever and one from a rat—were used for this purpose. Agglutinations using the patient's organism as antigen were obtained in all three serums in a titer of 1:6400. Agglutinin absorption tests were set up to determine whether the freshly isolated strain was identical with the other three. Two of them proved to be identical with the patient's organism. The third strain was a distinctly different type.

Agglutination tests, in which the patient's organism was run against his own serum, showed a marked rise in titer of immune bodies. None were found on June 15, but the titer had risen to 1:160 on July 3 and to 1:320 on July 27. Parallel agglutination tests on the first two dates were negative with dysentery polyvalent, *Pasteurella tularensis* and *Brucella abortus* antiserums.

On first isolation the organism showed a pronounced virulence for mice. 0.5 cc of a 24-hour culture in 10 per cent ascitic broth, when injected into each of 5 mice intraperitoneally, led to death in 24 hours. After repeated transfers the mouse virulence was lost. The *Streptobacillus* was markedly pleomorphic in the peritoneal cavity, but appeared as short, gram-negative rods when isolated by smear from the heart's blood†.

A penicillin sensitivity test revealed that the organism was killed by an in vitro concentration of 0.0156 units per cubic centimeter‡.

Subsequent blood cultures on June 19 and July 3 showed no growth.

This patient did not show any of the characteristic clinical signs of rat-bite fever. Since massive doses of penicillin were begun within twenty-four hours of the onset of the illness, however, and since the *Streptobacillus* isolated was extremely sensitive to the drug, the absence of such findings is not surprising. The illness began after a characteristic incubation period following the rat bite. Isolation in pure culture and the demonstration of a significant rise in titer of agglutinins during convalescence demonstrated that the infection was caused by

Str. moniliformis. The course of the disease did not favor an attempt to isolate *Spirillum minus*.

The outstanding feature of infections due to *Str. moniliformis* is the predilection of this organism for synovial membranes, which results in a migrating polyarthritis. Arthritis is characteristic of spontaneous outbreaks of the disease in mice⁷. Budding⁹ has recently shown that the *Streptobacillus*, when inoculated onto the chorioallantoic membrane of the chick embryo, leads to pathologic lesions that are localized primarily in the joints. Joint involvement is not invariably present in this type of rat-bite fever, although it occurs in a high percentage of cases.

In the cases presented above the characteristic manifestations of rat-bite fever did not appear. The early institution of penicillin treatment may explain the short course in Case 2. In Case 1 it is possible that the organism was of low virulence. One may also speculate that in some cases the infection is limited to a mild bacteremia. This might be found if patients coming to a surgical outpatient department for rat-bite treatment were subsequently followed with blood cultures.

The efficacy of penicillin treatment in cases of rat-bite fever has been described by a number of authors. Altemeier and his co-workers¹⁰ and Wheeler¹¹ noted rapid clinical improvement with penicillin. The sensitivity of the organism in Case 2 puts it in the range of bacteria most susceptible to the drug, such as pneumococci and streptococci.

Contrary to the experience of Brown and Nunemaker,⁵ the culture of *Str. moniliformis* has not been found difficult. Meat-infusion broth is sufficient for blood culture on primary isolation. The best growth, however, is obtained in infusion broth with the addition of 10 to 15 per cent ascitic fluid. Within twenty-four hours the growth appears as large aggregates of colonies near the bottom, suspended in a clear liquid. The organism can be maintained on blood-agar plates incubated in a candle jar. Transfers at weekly intervals have been sufficient to maintain three different strains for several years.

In Case 2 the agglutination titers rose to 1:160 and 1:320, although the patient had apparently harbored the *Streptobacillus* for only a short time. Brown and Nunemaker⁵ concluded from a serologic study of the serums from 120 control cases that a titer of 1:80 or above was definitely diagnostic of infection with *Str. moniliformis*. The natural growth of the *Streptobacillus* as aggregates of colonies in broth is unsuitable for the performance of agglutination tests. Suitable suspensions of antigen were obtained when a twenty-four-hour broth culture was agitated in a shaker for thirty minutes at moderate speed.

"Rat-bite fever" is a term used to cover two separate infections—one caused by *Str. moniliformis*

*Acknowledgment is made to Miss Marion E. Lamb, bacteriologist, Boston City Hospital, for her helpful suggestions regarding the bacteriology in this case.

†This phenomenon has been described by Parker and Hudson.⁴

‡Test performed through the courtesy of Miss Clara Wilcox, Thorndike Memorial Laboratory, Boston City Hospital.

and the other by *S minus*. The diseases caused by these organisms may be clinically indistinguishable, owing to overlapping symptomatology. Both respond well to penicillin therapy. Dawson and Hobby,¹² supported in a discussion by Blake, have questioned whether the laboratory evidence has been sufficient in all reported cases to support a diagnosis of infection with *S minus*, since mice used for blood inoculations may naturally harbor the *Spirlillum*. It has been established by inoculations of parietic patients with *S minus*, however, that this organism can cause a disease in man with both skin rash and polyarthritis.^{13 14} One wonders, nevertheless, whether the *Streptobacillus* might not be found more often if properly looked for in cases of rat-bite fever. No case reports have been found in the literature in which both organisms were found. Brown and Nunemaker⁵ present evidence that *Str moniliformis* is the most frequent infecting agent following rat bite.

SUMMARY

Two cases of infection with *Streptobacillus moniliformis* are reported. The simplicity of culturing

this organism and of agglutination tests is stressed. Penicillin was extremely effective in 1 case.

REFERENCES

1. Levaditi C, Nicolau S, and Poineloux P. Sur le rôle étiologique de streptobacillus moniliformis (nov spec) dans l'érythème polymorphe aigu septicémique. *Compt. Rend Acad d Sc* 180 1188-1190 1925
2. Hazard, J B and Goodkind R. Haverhill fever (erythema arthriticum epidemicum) case report and bacteriologic study. *J A M A* 99 554-558 1932
3. Place E H, Sutton, L E Jr., and Willner O. Erythema arthriticum epidemicum preliminary report. *B Mo M & S J* 194 285 287 1926
4. Parer F Jr and Hudson N P. Etiology of Haverhill fever (erythema arthriticum epidemicum). *Am J Path* 2 357-359 1926
5. Brown T M., and Nunemaker J C. Rat bite fever: review of American cases with re-evaluation of etiology: report of cases. *Bull Johns Hopkins Hosp* 70 201-227 1942
6. Watkins C G. Rat bite fever. *J Pediat* 28 429-448 1946
7. Levaditi C, Selbie R F, and Schoen R. Le rhumatisme infectieux spontané de la souris provoqué par le Streptobacillus moniliformis. *Arch Inst Pasteur* 48 308-343 1922
8. van Roovan C E. Biology pathogenesis and classification of Streptobacillus moniliformis. *J Path & Bact* 43 455-472 1936
9. Buddingh G I. Experimental Streptobacillus moniliformis arthritis in chick embryo. *J Exper Med* 80 59-64 1944
10. Altmeier W A., Snyder H and Howe G. Penicillin therapy in rat bite fever. *J A M A* 127 270-273 1945
11. Wheeler W E. Treatment of rat bite fevers with penicillin. *Am J Dis Child* 69 215-220 1945
12. Dawson M H and Hobby G L. Rat-bite fever. *Tr A A-Physicians* 54 329-332 1956
13. Solomon H C, Bo L A, Theiler M and Clay C L. Use of sodoku in treatment of general paralysis preliminary report. *Arch Int Med* 38 391-404 1926
14. Hershfield A S, Kibler C A, Colby S, Koenig M T, Schmid O W, and Saunders M. Sodoku treatment in paresis preliminary report. *J A M A* 92 772 1929

SURGICAL TREATMENT OF DEGENERATIVE ARTHRITIS OF THE KNEE JOINT*

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SINCE the conservative treatment of degenerative or hypertrophic arthritis of the knee joint had been disappointing at the Lahey Clinic, particularly in vigorous patients with unilateral involvement, a plan of surgical management was decided on, and in 1940 the results obtained in knee joints that had been operated on in 20 cases were reported.¹ Since then sufficient time has elapsed to evaluate the results in an additional 10 cases. The object of this paper is to discuss criteria for selection of patients for surgery, to present details of the operative technic and finally to report the results obtained.

Selection of Patients

The importance of careful selection of patients for knee-joint surgery, especially when joint function is maintained, cannot be too strongly emphasized. In each case a detailed medical examination is carried out, and if the physical status indicates that major surgery on the knee is feasible, in addition to the orthopedic survey, the patient is considered from the standpoint of his ability to co-operate

and to follow out tiresome and often painful exercises, and in particular, an estimate is made of his desire or drive to return to comparatively normal activities. Provided that the patient's physical condition permits major surgery on the knee and the other requirements are fulfilled, operation is advised. It is understood that of many patients who have degenerative arthritis of the knee joint, relatively few meet the standards for surgery as herein described. But if the cases are carefully selected on the basis of the points outlined, the results have been superior to those obtained with other methods.

In patients with unilateral joint involvement in whom the preoperative studies indicate an advanced destruction of the joint, the significance of these data is emphasized, the patient is advised to permit an arthrodesis if on joint visualization the preoperative impressions are confirmed.

Operative Technic

The knee joint was first explored through a medium parapatellar incision. Later, in patients with marked hyperplasia of the patella, a midline incision was employed, the patella removed by sharp dissection, and the remainder of the operation performed under excellent visualization. In cases

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with advanced degenerative changes that indicated possible arthrodesis, the inverted "V" incision in the capsule, as described by Coonse and Adams,² has been most satisfactory

In the planning of a surgical procedure for the treatment of degenerative arthritis of the knee joint, repeated clinical observations indicated that the following structures in particular were to be considered the hyperplastic synovial membrane, the patella, the articular cartilage covering the femur and tibia and marginal exostoses, and the menisci.

If definitely scarred and hyperplastic, the synovial membrane was removed from the anterior portion of the joint, together with the fat pad. In none of these patients was the posterior compartment explored. Likewise, when the menisci were degenerated, they were carefully excised back to the posterior attachment.

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The remaining steps of the operation comprise removal of marginal exostoses and shaving down of the fibrillated cartilage over the articular surfaces of the femur and tibia. This cartilage is often markedly degenerated, and it should be shaved down to a firm base, the operator should ensure that there are no rough spots to cause irritation. In this connection Magnuson,⁵ in 1941, reported good results in a large series of cases in which synovectomy was not performed and in which the patella was never entirely removed. This author emphasized that "the success of the procedure depends on the complete removal of all mechanical irritants from the joints." I am in complete accord with this statement and for that reason believe that in patients with long-standing, pronounced chronic hyperplasia the synovial membranes should be

taken out and the patella either cut down or removed.

The joint capsule is closed with interrupted silk, the subcutaneous tissue with interrupted fine chromic, and the skin with wire sutures. Use of the last material permits the sutures to remain in place ten to fourteen days postoperatively, while active muscle exercises and motion in the joint are instituted. The resultant scars have been much less obvious than when the skin was closed with other types of sutures. Large, fluffy sections of gauze pads are placed about the knee, and a firm pressure bandage applied to the entire extremity. Initially, patients are more comfortable in a plaster cast, but return of joint motion is delayed in comparison with cases in which only a pressure bandage is utilized.

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Postoperative Care

In the average case motion was begun on the fourth or the fifth day. Patients with adequate muscle control, particularly if they had received adequate preoperative training in muscle exercise, began motion on the third day. In others, motion was begun later. In all patients the extremity was intermittently suspended just above the ankle region by a sling attached to an elastic cord from an overhead frame. This permitted relatively early active exercise with a minimum degree of discomfort. Local heat and light massage were routinely carried out. Weight bearing was started within two weeks, under careful guidance. In an average of 3 out of 4 patients, gentle manipulation of the knee joint was performed under intravenous Pentothal anesthesia within three weeks after operation. It was found that this step materially expedited

return of normal joint flexion With one exception there were no untoward reactions following this maneuver

Results

With the objective of maintaining knee motion, 30 patients were operated on, and in 5 additional patients an arthrodesis was performed. In each case only one knee was treated. The average age of this group was fifty-seven years. There were failures in 3 cases. One has already been reported as being due to the presence of a mixed arthritis¹, 2 patients did not co-operate in carrying out the postoperative exercise regimen. Of the 5 patients submitted to arthrodesis, a firm bone fusion was obtained in each knee joint. The follow-up period ranged from seventeen months to seven years, with an average of twenty-six months.

Of the remaining 27 patients operated on to improve joint function, all exhibited postoperative increase of knee motion. Normal active extension of the lower leg on the thigh was observed in all cases. The minimum range of flexion was 65°, whereas the maximum was normal. In this group, 21 patients had a normal range of motion. In every case the articulation was stable, and swelling of the knee was not observed. Twelve patients denied any symptoms referable to the joint, 8 reported intimate aching pain in the knee after exposure to severe cold and damp weather. Seven patients described intervals of apparently mild discomfort after a rest period preceded by marked physical activity.

In summary, all this group emphasized that they did not suffer severe pain and that their symptoms were in no sense comparable to those experienced before operation.

With the exception of a case previously reported, the follow-up roentgenogram showed essentially no change as compared with the immediate postoperative film, and in no case did the subsequent film reveal the pronounced degenerative arthritis evidenced in the preoperative roentgenogram.

* * *

In patients with pronounced disability due to degenerative arthritis of the knee joint, who had been selected on the basis of their physical fitness for operation and in particular for their willingness to co-operate with the postoperative regimen described above, and with the objective of maintaining knee motion, the surgical procedure detailed in the text resulted in marked amelioration of symptoms. In a smaller group of patients who were incapacitated because of marked destruction of the joint as shown at operation, arthrodesis resulted in complete relief of pain while allowing greatly increased physical activity. Over a follow-up interval ranging from seventeen months to seven years, observations on this group of 35 patients confirm the belief that the surgical treatment of degenerative arthritis deserves an important place in the physician's armamentarium.

REFERENCES

- 1 Haggart, G. E. Surgical treatment of degenerative arthritis of knee joint. *J. Bone & Joint Surg.* 22:717-729 1940.
- 2 Coonse, K., and Adams, J. D. New operative approach to knee joint. *Surg. Gynec. & Obst.* 77:344-347 1943.
- 3 Keefer, C. S., Parker, F. Jr., Myers, W. K., and Irwin, R. L. Relationship between anatomic changes in knee joint with advancing age and degenerative arthritis. *Arch. Int. Med.* 53:325-344 1934.
- 4 Brooke, R. Treatment of fractured patella by excision: study of morphology and function. *Brit. J. Surg.* 24:733-747, 1937.
- 5 Magnuson, P. B. Joint debridement: surgical treatment of degenerative arthritis. *Surg., Gynec. & Obst.* 73:1-9 1941.
- 6 Haggart, G. E., and Thomas, G. L. Use of Stader splint in arthrodesis of knee joint (preliminary report). *Lakey Clin. Bull.* 4:85-89 1945.
- 7 McKeever, D. C. Use of cellophane as interposition membrane in synovectomy. *J. Bone & Joint Surg.* 25:576-580 1943.

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pollen, but only after subsequent exposure. In animal experiments no anaphylactic reactions were observed unless the animals had previously been sensitized to the fava bean by means of feeding or by injection of extracts.

The exact mechanism of how the hemolysis is produced is not too well understood. Preti⁶ reports that even sucklings were afflicted when the mother or the wet nurse ate fava beans, and in his cases the mother did not necessarily present the symptoms herself. He also noted that the condition was rare in persons who ate fava beans regularly throughout the year, and he assumed that this was due to a desensitization.

The incubation time between inhalation or ingestion and the onset of the first symptoms may be one to three days or only a few minutes. Thus, McCrae and Ullery's⁷ patient stated that he became unconscious while walking through the blossoming fields.

The usual prodromal symptoms include fatigue, weakness, headache, pain in the upper or lower extremities, anorexia, nausea, vomiting, abdominal pain, diarrhea and, in severe cases, unconsciousness. From one hour to one or two days after these manifestations hemoglobinuria begins, with marked prostration and at times with shock. At the same time the skin shows an ashen-gray pallor simultaneous with a moderate jaundice.

Depending on the degree of severity there are, according to Gasbarrini, five different forms: the abortive form, which is characterized by headache, nausea, pain in the upper and lower extremities, pallor of the skin and mucous membranes and absence of hemoglobinuria, the mild form, which is characterized by these symptoms, in addition to moderate anemia, slight icterus, slight hemoglobinuria and, usually, spontaneous recovery within a week, in the grave form, which may be deadly and which strikes soon after the ingestion of fava beans, the patient presents extreme weakness and prostration, marked pallor and moderate icterus of the skin and scant and markedly bloody urine — children often suffer from diarrhea and vomiting of bile, the fulminant form, which principally affects children and presents a sudden and intense anemia and hemoglobinuria and in which death from shock frequently occurs within the first twenty-four to forty-eight hours, and the so-called "hemorrhagic form," which is characterized by petechiae and ecchymoses and is extremely rare and nearly always fatal.

On physical examination an enlarged spleen may or may not be found. The liver is often slightly enlarged and moderately tender. The other abdominal organs usually do not show any pathologic change. Except in the rare hemorrhagic form there are no cutaneous manifestations of hemorrhage. The scleras are moderately jaundiced, and the skin shows the combination of pallor and icterus

described above. The patient is usually apathetic and listless, and may be in profound shock.

The blood picture is that of a severe normocytic anemia and the hemoglobin may be as low as 20 per cent and the red-cell count as low as 1,000,000. Some anisocytosis, poikilocytosis and polychromatophilia are present, but neither spherocytes nor target or oval cells have been reported. The fragility of erythrocytes to hypotonic sodium chloride solutions is usually within normal limits. Tests for acid, mechanical and heat fragility^{9, 10} have apparently never been made in this condition.

In the initial stage the blood reveals a leukopenia, a neutropenia and a thrombocytopenia. Shortly thereafter leukocytosis begins, and the blood may even present a leukemoid picture. The platelets also begin to increase in number and may go as high as 900,000, which according to Preti⁶ gives the case a favorable prognosis.

The blood chemical findings usually indicate a markedly increased icteric index, a moderate to marked bilirubinemia and a negative direct and a positive indirect van den Bergh reaction.

The urine may vary from a slight pinkish discoloration in abortive cases to a deep brick red in the severer forms. It may contain a few red cells and usually reveals a +++ test for albumin and a number of casts. The guaiac test is often ++++. The urine and stool show a moderate to marked increase of urobilinogen, the stool is brown, and the urine may contain some bile pigment.

In spite of its stormy and alarming onset, favism is a comparatively benign disease. The majority of patients recover. The mortality rate is 8 per cent, death occurring either in the initial stage of shock or later from anemia. The clinical course is apparently not influenced by the amount of ingested beans, minimal amounts having led to quite protracted illness and large portions having been followed by rather speedy recoveries. McCrae and Ullery's⁷ patient required hospitalization for thirty-eight days, whereas Hutton's patient was out of bed on the fifteenth hospital day.

No treatment may be required in the abortive cases, but in the severer forms, the most effective therapy is the immediate institution of compatible blood transfusions. These transfusions should be repeated daily as long as hemoglobinuria and other evidence of erythroclastic activity are present. For the initial stage of shock adrenalin has been recommended. The obvious prophylaxis is for the hypersensitive subject to avoid ingestion of the bean or inhalation of its pollen.

In the following case transfusions of whole citrated blood resulted in recovery.

A 3½-year-old, American-born boy of Italian extraction was admitted to the hospital on July 29, 1946, with the chief complaint of "bloody urine" of 16 hours' duration. The history, as obtained from the somewhat panicky parents, revealed that on the evening prior to admission the child had expressed a desire to urinate but had stated that he

FAVISM*

A Short Review and Report of a Case

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FAVISM is an acute hemolytic anemia following contact with beans or pollen of *Vicia faba*. It has been classified among the paroxysmal hemoglobinurias,¹ and manifests itself by the so-called "hemolytic syndrome," which, in view of its specific action on the red cells, might better be named the "erythroclastic syndrome." The main characteristics are a fulminant onset, jaundice, anemia and hemoglobinuria. Favism is probably an allergic phenomenon that is due to a hypersensitivity to the ingestion of the beans or to inhalation of the pollen of *V. faba*, a large yellowish bean of the lima-bean family.

The condition is exceedingly rare in the United States, although not infrequent in Sicily, Sardinia and southern Italy. Apparently, only 2 cases have been reported in English, and these occurred in Italian-born adults who had immigrated to the United States.² The case reported below therefore appears to be the first case in an American-born child, although the patient was of Italian extraction.

Favism is a comparatively old disease. It was known to Herodotus, Pythagoras and Empedocles, and the condition is stated to have been quite widespread and grave, at times, in ancient Egypt and other Mediterranean countries.³ The first modern authors to report it were Messina in 1851, La Grega in 1856 and Di Pietra in 1858. The first to forward the idea that favism was due to an idiosyncrasy was Bertòlo in 1873.

An excellent paper about favism was written by Gasbarrini,⁴ who found a hereditary factor in about 20 per cent of cases. He observed that neuropathic, anemic and "lymphatic" persons were somewhat predisposed to the affliction. Gasbarrini refuted the theory of the older Italian authors that favism was caused by an infectious agent — possibly a fungous infection of the bean — and attributed the disease to a "toxin." A similar opinion was held by Fermi and Martinetti,^{4, 5} who reviewed 1211 cases.

Preti,⁶ who, as director of the University Clinic of Sassari in Sardinia, had ample occasion to observe a number of cases, maintained that the theory of a toxin was untenable because of the bizarre way in which the disease struck. He believed that favism was caused by an anaphylactic reaction.

The first of the cases in the English language mentioned above was reported by McCrae and Ullery,⁷ who described a rather severe attack of

hemoglobinuria and the usual symptomatology following the ingestion of fava beans in a fifty-three-year-old Italian-born man. In his youth the patient had had several episodes of unconsciousness while walking through fields of blossoming fava plants in Sicily, all these episodes had been followed by hemoglobinuria. After a diagnostic skin test this patient had a recurrence of some of the symptoms. The second case, reported by Hutton,⁸ occurred in a twenty-year-old Italian-born man who, besides the usual symptomatology, had a definite family history of occurrence in his grandfather, grandmother, mother and a brother. This patient gave a negative skin test.

The majority of cases have been reported from Sicily, Sardinia and the southern provinces of Italy. There are also a few reports from Germany.

Favism has quite a definite seasonal incidence, most cases being observed between April, the season of blossoming of the plant, and June to July, when the fresh, mature bean appears on the market. Gasbarrini⁴ noted that prolonged rain hindered the development of favism in a given year.

Heredity seems to play a definite role in about 20 per cent of cases. There are reports of entire families who are hypersensitive to the fava bean, as in Hutton's⁸ report. In the remaining 80 per cent no hereditary factor is evident. There is apparently no predilection for either sex, both being affected about equally. The majority of cases occur during childhood and adolescence, but the disease is by no means limited to the first two decades of life and cases have been reported in elderly people.

In the series of 1211 cases reported by Fermi and Martinetti,⁴ 459 were caused by inhalation of the pollen from the blossom of the plant, 725 were due to ingestion of the bean, and 27 had an undetermined etiology. Autopsies have been recorded in only 2 cases, in both of which the exact mechanism of the pathogenesis was rather inconclusive.³ Both examinations showed a generalized hyperemia and an increase in the size of the liver, the kidneys and the spleen. The spleen was reported as being three times its normal size in 1 case. According to Hoffman and Kracke,¹ a hypersensitivity to one of the protein substances present in the pollen as well as in the bean is created through repeated contact — either by inhalation or by ingestion — and is followed by destruction of erythrocytes, leading to the hemolytic-hemoglobinuric syndrome. The authors maintain that the syndrome does not occur on the first contact with the bean or its

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fava beans or inhalation of the pollen is obtainable. In the case presented above, that of an American child with an emphatic denial of contact with *V. faba*, the diagnosis was not made at first. After all known erythroclastic (hemolytic) syndromes had been ruled out, an erroneous admission diagnosis of acute hemolytic anemia of the Lederer type was made, the diagnosis was changed only on the third hospital day, when a history of ingestion of fava beans was elicited.

Such an error is understandable, since the onset, clinical picture and clinical course of Lederer's anemia¹⁶ are similar to those in the case presented above, for that reason the disease has been called *anémie en coup d'archet* by French authors.¹⁷ It is quite possible that some of the less well understood of the 60 cases of Lederer's anemia reported in the literature^{18, 19} — whose etiology is unknown and was attributed by Lederer himself to an infectious process — can be explained by an allergic phenomenon similar to or even identical with that in the case presented above. Since fava beans are regularly eaten by a large number of people without producing symptoms, even in the person who may suddenly develop a marked erythroclastic process, it seems not improbable that a previous fava bean meal has been forgotten by the patient and escaped the attention of the physician.

SUMMARY

A case of favism that is apparently the first reported in an American-born child is presented. In two previous reports in the literature in English, both cases occurred in immigrants who had been born in southern Italy.

The diagnosis of favism was not made initially because the anxiety-stricken parents denied that the patient had eaten fava beans. This was ad-

mitted only on the third hospital day, after which the diagnosis was apparent.

The question is raised whether some of the obscure cases of acute hemolytic anemia of undetermined origin in the literature had a similar etiology.

In the case presented the onset of the condition was alarming, but the patient's response to daily blood transfusions was such that in eight days he was discharged from the hospital entirely recovered.

REFERENCES

- 1 Hoffman B J and Kracke R. R. Hemoglobinuria. *Clinics* 2:179-200 1943
- 2 Kracke R. R. *Diseases of the Blood and Atlas of Hematology with Clinical and Hematologic Descriptions of the Blood Diseases including a Section on Technic and Terminology*. Second edition. 692 pp. Philadelphia J. B. Lippincott Co. 1941
- 3 Gasbarri A. Il favismo. *Policlinico (sez. prat.)* 22:1505-1512 and 1517-1541 1915
- 4 Ferri C., and Maroncelli P. Ricerche isturite sul favismo. *Policlinico (sez. prat.)* 8:1112 1902
- 5 Idem. Studio sul favismo. *Arch. Exp. Med.* 15:75-134 1905
- 6 Prell L. Über den sogenannten Fabismus. *Klin. Wochenschr.* 6:2429-2432 1927
- 7 McCrae T. and Ullery J. C. Favism: report of case. *J. A. M. A.* 101:1389-191 1933
- 8 Hutton J. E. Favism: unusually observed type of hemolytic anemia. *J. A. M. A.* 109:1618-1620 1937
- 9 Ham T. H. Studies on destruction of red blood cells. I. Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria: investigation of mechanism of hemolysis with observations on five cases. *Arch. Int. Med.* 64:1271-1303 1939
- 10 Dameshek W. Hematology. *New Eng. J. Med.* 232:250-257 and 260-266 1945
- 11 Dameshek W., and Schwartz S. O. Hemolysis as cause of clinical and experimental hemolytic anemias with particular reference to nature of spherocytes and increased fragility. *Am. J. M. Sc.* 196:769-792 1938
- 12 Dameshek W. Familial hemolytic crisis: report of two cases occurring within ten days. *New Eng. J. Med.* 224:52-56 1941
- 13 Idem. Hematology. *New Eng. J. Med.* 228:157-164 and 188-197 1943
- 14 Canbr C. B., Carpenter G., and Ellmore L. F. Drepanocytes (sickle cells) and apparently acute surgical condition of abdomen: report of their occurrence in white youth with laparotomy. *Arch. Surg.* 48:121-123 1944
- 15 Lederer M. Form of acute hemolytic anemia probably of infectious origin. *Am. J. M. Sc.* 70:500-510 1925
- 16 Giordano A. S. and Blum L. L. Acute hemolytic anemia (Lederer type). *Am. J. M. Sc.* 194:511-526 1937
- 17 Fieissinger N., Decourt P., and Laur C. M. Les anémies hémolytiques aiguës. *Scand. J. Clin. Lab. Invest.* 5:257-270 1951
- 18 MacIntosh A. H., and Cleland J. B. Cited by Giordano and Blum.¹⁶
- 19 Morawitz P. Über atypische schwere Anämien. *Deutsches Arch. f. Klin. Med.* 88:493-508 1907

had pain in both knees and was too weak to walk to the bathroom. The mother had carried the child to the bathroom and had noticed that the urine was bloody. The family physician stated that the urine showed a +++ test for albumin but that he was unable to find any blood cells on microscopical examination. The bloody color of the urine increased in intensity during the night and the following morning, and the mother noticed that the skin had become somewhat jaundiced. The patient's general condition grew worse, he became more and more prostrated, and at noon, when he was admitted to the hospital, he appeared in extremis.

Both parents were exhaustively questioned about the past history in an effort to obtain a lead regarding the nature of the condition. They denied any instance of a similar episode in any of the close or remote members of the family at any time. There was no history of exposure to malaria, of syphilis or antisyphilitic treatment, of exposure to cold, of swimming at the beach, of any physical exertion, of sulfonamide or acetanilid medication or of contact with lead, other blood-destroying chemicals or carbon monoxide. There was no history of a spider or a snake bite or of ingestion of mushrooms or of fava beans. The child had been in good health since birth, no anemia having appeared before the present episode.

Physical examination revealed a well developed and well nourished boy who appeared to be moribund. He was extremely weak, apathetic, listless and, at the same time, irritable. The skin was both markedly anemic and markedly icteric, showing a combination of an ashen-gray pallor and a deep jaundice. The head was essentially normal except for moderately jaundiced scleras. The conjunctivas and other mucous membranes were extremely pale. The ears, nose and throat were essentially normal. There was no cervical or other adenopathy. The trachea was in the midline, the thyroid gland was not palpable. The chest was clear and resonant to percussion and auscultation, and there were no audible rales. The cardiovascular system presented a marked tachycardia (160 per minute), a regular sinus rhythm, no enlargement of the heart, no murmurs and no thrills. The heart sounds were of good quality. The abdomen was soft and nontender, and no masses were felt. The liver was slightly enlarged, the edge extending 1 cm below the costal margin, the spleen was not palpable. The extremities were essentially normal. The skin presented no pathologic changes except the discoloration described above. There were no petechiae, ecchymoses, evidence of insect or snake bites or interruption of the continuity of the skin at any place. The reflexes were physiologic.

The temperature was 102°F, the pulse 160, and the respirations 30.

Examination of the blood showed a red-cell count of 1,140,000, with a hemoglobin of 4.2 gm (29 per cent), and a white-cell count of 20,500, with 72 per cent neutrophils, 24 per cent small lymphocytes, 2 per cent monocytes, 1 per cent eosinophils, 1 per cent basophils and 1 per cent normoblasts. There was slight anisocytosis and moderate polychromatophilia. The platelet count was 248,000. The bleeding time was 90 seconds, and the clotting time 150 seconds. No spherocytes or target, oval or sickle cells were seen. There was no latent sickling. The mean corpuscular volume was 91 cu microns. The reticulocyte count was 4.2 per cent. The blood group was AB, and the patient was Rh+. A fragility test showed initial hemolysis at 0.44 in the patient and at 0.40 in the control and complete hemolysis at 0.28 in the patient and at 0.32 in the control. The icteric index was 57 units. The van den Bergh test showed a negative direct and a positive indirect reaction. A stool was negative for blood but positive for bile. The urine revealed an increased urobilinogen and some bile. It was positive for albumin and negative for sugar, and the sediment showed many coarse granular casts. The guaiac reaction was + + + +, but no red cells were found in the urine.

It was evident that there was, not hematuria, but hemoglobinuria, which is, of course, nothing but the urinary manifestation of marked red-cell destruction, and consequently a hemolytic or erythroclastic syndrome whose origin was obscure. A hemolytic crisis of a familial congenital hemolytic anemia was ruled out by the absence of spherocytes, of an enlarged spleen, of a pre-existing mild anemia and of a positive family history.¹¹

The blood picture was neither that of a Cooley's anemia (thalassemia or Mediterranean syndrome) nor that of a sickle-cell anemia,¹² the latter being considered as a possibility because it occurs occasionally in patients of Italian extraction.¹⁴ The condition was too acute and too alarming for a Marchiafava-Michele syndrome, and from the history, black-water fever, cold hemoglobinuria, march hemoglobinuria, favism or toxic hemolysis of any known mechanism could be excluded. The only condition that seemed to fit this case appeared to be Lederer's anemia,¹⁵ a condition that has often been misused as a catchall for hemolytic syndromes that cannot otherwise be classified.

Fortunately, on the 3rd hospital day, the mother, who had recovered from her initial panic, remembered that on the day of the onset of the disease the child had had a large meal of fava beans. She admitted that she had "forgotten all about it" owing to the excitement about the child's alarming condition. Consequently, the diagnosis was changed from acute hemolytic anemia of the Lederer type to favism. This revelation did not affect the therapy or the clinical course in any way, since the treatment for both conditions is identical.

Immediately after admission a transfusion of 300 cc of whole citrated blood was given. Toward the end of the transfusion the temperature rose to 106.8°F, following a chill of 10 minutes' duration and a convulsion lasting about 2 minutes. The pulse was 160, and the respirations went up to 60 and were labored. A moderate cyanosis was observed. The rise in temperature was probably a transfusion reaction, but because the diagnosis was uncertain it was considered advisable to administer 50,000 units of penicillin initially and 25,000 units every 3 hours.

On the following day the whole picture had changed rather dramatically. There was still the same amount of hemoglobinuria, with increased urobilinogen, and a + + + + guaiac reaction, but the temperature had fallen to 100.4°F, the pulse to 120, and the respirations to 40. The color of the skin was definitely improved, with less anemia and no cyanosis. The hemoglobin had risen to 7.6 gm (52 per cent), and the red-cell count to 2,400,000. The patient was less apathetic and began to answer when spoken to.

For 5 consecutive days 250 cc of whole citrated blood was administered daily with a consistent change in the blood picture (Table 1). The clinical condition continued to improve

TABLE 1 Significant Laboratory Data

HOSPITAL DAY	RED CELL COUNT	HEMOGLOBIN	
	$\times 10^6$	gm	%
1	1.1	4.2	29
2	2.4	7.6	52
3	3.0	8.5	58
4	3.8	10.7	74
5	4.1	12.2	84
8	4.7	13.1	90

rapidly, and the temperature fell to and remained at normal levels, the hemoglobinuria disappeared, the urobilinogen value becoming normal on the 4th day. The jaundice and anemia cleared up gradually, and on the 8th hospital day the patient was discharged.

An interesting feature in this case was presented by the spleen, which on the day of admission was not palpable. On the second hospital day a slight enlargement appeared, and on the third day the spleen was definitely firm and enlarged, the edge extending two fingerbreadths below the costal margin and being rounded. The size of the spleen remained unchanged until the sixth hospital day, when it became softer and decreased until it was no longer palpable on the eighth day.

The diagnosis of favism is said to be easy when it occurs in one of the usually stricken regions of southern Italy and when a history of ingestion of

with gross congenital deformities. This relatively low virulence in mortality of the fetus becomes a greater calamity through a relatively high morbidity with subsequent serious defects.

Congenital Anomalies

In 1941 Gregg¹ reported a series of 78 cases of congenital cataract in which 13 patients were seen in his own practice. A definite history of rubella during pregnancy was obtained in 68 cases, and in the remaining 10 there was a suspicious history of rubella, although a definite diagnosis could not be established. Forty-four children presented evidence of congenital heart lesions, and patent ductus arteriosus was shown at autopsy in 3 cases. A characteristic of many of these infants was that they were poorly nourished and presented difficult feeding problems. This discovery by Gregg resulted from his correlating the finding of so many congenital cataracts with the fact that a rubella epidemic of unusual proportions had been in progress in Australia in the preceding year. In looking backward for an antenatal explanation he found that this relatively minor exanthematous disease had been an almost consistent factor during pregnancy.

Under the direction of the National and Medical Research Council of Australia a survey was instituted under the direction of Swan and his associates⁷² in South Australia. Their report on 61 children, covering the period from 1939 to 1942, inclusive, revealed that 49 mothers who had suffered an attack of rubella during pregnancy gave birth to 31 infants with congenital defects. Among the mothers of these defective children, 29 had had rubella in the first three months of pregnancy, and the 25 who had had the disease in the first two months of pregnancy gave birth to infants with congenital defects. Four of the 8 mothers who had had rubella in the third month gave birth to congenitally defective infants. Two defective children were born of mothers who had had rubella after the third month. As opposed to the 31 defective children 18 healthy children were born of these 49 mothers. Four cases of congenital cataract were found in which the mother denied any history of an exanthem during pregnancy. The relation between the month in which rubella was contracted and the occurrence of congenital defects is demonstrated in Table 1.

As in the Gregg report the majority of the children were poorly developed and presented feeding problems. In this series, however, the cardiac defects predominated: there were 17 infants with heart lesions, and 14 with eye defects. Seven were deaf mutes, and 4 showed mental retardation. The defects frequently appeared in combination. Among the 17 patients exhibiting cardiac lesions there were 8 who also had cataracts and 2 who were also deaf mutes. These striking combinations were

revealed in later reports and constitute the suggestion of a syndrome of rubella effects.

Further reports from Australia by Swan and his associates,⁷³⁻⁷⁴ Gregg and his co-workers,⁷⁵ Evans,⁷⁶ Carruthers,⁷⁷ Welch⁷⁸ and Vickery⁷⁹ strengthened the conviction that rubella was an etiologic agent of prime importance in these congenital deformities.

Evans⁷⁶ investigated the dental abnormalities among the first group of children reported by Swan and his associates.⁷² In 34 infants whose mothers had had rubella during pregnancy there were 18

TABLE 1 *Relation between the Time of Contraction of Rubella during Pregnancy and the Occurrence of Congenital Defects*⁷⁴

STAGE OF PREGNANCY	NO OF INFANTS WITH CONGENITAL DEFECTS	NO OF HEALTHY CHILDREN	TOTAL
0 to 1	8	—	8
1 to 2	17	—	17
2 to 3	4	4	8
3 to 4	1	2	3
4 to 5	—	1	1
5 to 6	1	2	3
6 to 7	—	—	—
7 to 8	—	1	1
8 to 9	—	2	2
TOTAL	21	18	49

with dental defects of a major character, consisting of marked retardation of tooth eruptions, defective formation of the incisors and hypoplasia.

Carruthers⁷⁷ examined 17 of the cases of deafness found in the survey made by Gregg et al.⁷⁵ in New South Wales. The severity of the attack of rubella appeared to have no relation to the severity of damage in the ear. Most of the children gave some evidence of hearing over the tone range from 512 to 2048. Nine patients were given caloric labyrinthine tests with results that showed little deviation from the normal except that there was no vomiting even though nystagmus was induced. Post-mortem examination of one infant who died at the age of six and a half months and whose mother had suffered an attack of rubella in the first month of pregnancy disclosed underdevelopment, congenital cataracts and a patent ductus arteriosus. The ossicles of the middle ear were normal, but in both ears there was a total lack of differentiation of the primitive cells in the organ of Corti. Welch⁷⁸ supplied another study from New South Wales, covering 34 cases of congenital deafness in children born in 1938 to mothers who had had rubella in pregnancy. All these cases showed islands of deafness in the tone range.

From the pediatric point of view Vickery⁷⁹ studied the children of 20 mothers who had had rubella in the first three months of pregnancy. All were partially deaf and backward in speaking. Eleven were undersized and underweight. All infants presented problems in management, with sleeplessness and nervous irritability. Only 2 had congenital

MEDICAL PROGRESS

RUBELLA (GERMAN MEASLES) (Concluded)*

CONRAD WESSELHOEFT, M D †

BOSTON

Flibbertigibbet

In folklore congenital deformities were considered to be the result of extrinsic influences on the pregnant mother. Something she saw or some experience she underwent was thought to bring about the defect in her child. At the time when there was a general belief in witchcraft and calamities were ascribed to demoniacal influence, congenital deformities were supposed to be the result of the casting of a spell on the pregnant mother. *King Lear* contains the following reference: "That foul fiend, Flibbertigibbet. He begins at curfew, and walks till the first cock. He gives the web and the pin, squints the eye, and makes the harelip." The "web and the pin" is an old term for cataract. Flibbertigibbet was merely an unseen character referred to in a play, but people firmly believed in witchcraft in those days. The spell of a witch was thought to bring about all manner of ills to man and beast. Witch hunts were carried out to rid communities of those who were "possessed," as persons dangerous to the health of a community. The witch scare eventually subsided, but to this day the idea prevails to a certain extent that extrinsic influences can bring about congenital deformities.

The medical profession has been searching for intrinsic causes for these calamities in the newborn. Of late it has been shown that certain characteristics and congenital anomalies are derived from the genes. These include blood-group antigens, hemophilia and several other conditions,⁶⁸ and animal experiments have shown that a lack of vitamin A early in pregnancy can bring about cataract.^{66, 67} It now appears that prenatal infection can so disturb the development of the eye and other organs of the body as to cause gross deformities. The Flibbertigibbet of today responsible for at least some congenital defects seems to be the virus of rubella, which stalks unseen by day as well as by night in the house, the school-room and crowded places and which until recently was quite unsuspected and unfearful.

Miscarriage and Stillbirth

An obstetrician, Dr. Raymond B. Titus, asked me to see a primipara with a typical attack of rubella in the third month of pregnancy. The attack appeared to pass off in an uneventful manner.

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Six months later Dr. Burnet, of Australia, informed me of the dangers of rubella to the fetus. From Dr. Titus I learned that the patient had subsequently miscarried. At about that time a twenty-three-year-old primipara was admitted to my service at the Haynes Memorial with rubella. She miscarried on the sixth hospital day. Through the courtesy of Drs. Dwight L. Siscoe and C. J. Dunlop I learned of a patient who suffered an attack of rubella in the first half of the second month of pregnancy. Quickening was recognized after the fourth month and then ceased to be present. With failure of the uterus to increase in size the death of the fetus was determined. A macerated fetus was delivered in the seventh month. The mother has since been delivered of a healthy infant. A miscarriage in the third month of pregnancy after an attack of rubella in the second month has been reported by Swan and Tostevin.⁶⁸ On examination of the fetus a unilateral cataract was found. Goar and Potts⁶⁹ describe twins at seven months from a mother who had rubella in the first month of pregnancy. One was stillborn, and the other twin lived but had bilateral cataracts and a congenital heart lesion. A stillbirth with hydrocephalus in the seventh month of pregnancy following an attack of rubella in the first month has been reported by Fox and Bortin.⁷⁰ These authors, however, present another side of the picture, reporting normal twins and 2 other normal babies born of mothers who had rubella in the second month of pregnancy, 3 normal infants of mothers who had rubella in the third month, 1 normal baby whose mother had rubella in the fourth month and 2 normal babies from mothers who had rubella in the seventh and ninth months. All the normal infants were born at full term.

Thus, following an attack of rubella, the mother may miscarry, may be delivered of a premature stillborn child with deformities, may be delivered of a living child with serious congenital deformities or may go to full term and give birth to a perfectly normal child.

A more serious virus disease, smallpox, is known to cause miscarriage, and some French authors⁷¹ have found this to occur in 50 to 60 per cent of cases. In relapsing fever, which is a rickettsial disease, a fetal mortality of 92.4 per cent has been recorded.⁷² It is possible that the lower virulence of the rubella virus enables the fetus to survive more frequently, but such a survival may lead to the birth of a child

the various surveys of Swan, Gregg and their many associates. This compilation deals with the relation of the time of contraction of rubella during pregnancy and the birth of defective and normal children. It will be seen that in general this conforms with Table 1. The results are startling. When rubella occurred in the first two months of pregnancy there were 118 infants with congenital defects and only 4 normal ones, whereas when the attack of rubella took place in the last five months of pregnancy there were 6 babies with congenital defects and 20 normal ones. This indicates that during the

surveys. None of these, however, compare with the figures supplied from Australia. Nevertheless, the combined results add greatly to the evidence that rubella in the early months of pregnancy is a serious problem.

The subject of the normal babies born of mothers who contracted rubella during pregnancy seemed to be worthy of further investigation. I have therefore assembled these in Table 3, combining the figures already utilized in Table 2 with those derived from America, giving a total of 48 normal infants. The figures are again arranged by months

TABLE 3 Normal Babies Born to Mothers Who Had Contracted Rubella during Pregnancy

AUTHOR	MONTH OF PREGNANCY								TOTAL
	0-1	1-2	2-3	3-4	4-5	5-6	6-7	8-9	
Swan et al. ⁷²			4	2	3	3		1	18
Swan et al. ⁷³						2			2
Swan et al. ⁷⁴		1		1		1			3
Swan et al. ^{75*}	1	1						1	4
Gregg et al. ⁷⁶	1		1	1	2	1	1		6
Fox and Bortin. ⁷⁰		4	3	1			1	1	10
Councilman†								1	1
Conte et al. ⁷¹								1	1
Aycock and Ingalls. ⁷⁷		1		1				1	3
Totals	2	7	8	6	—	—	5	4	48
Prendergast ⁸⁰ ‡			4						
First trimester			17						21
Second trimester			18						
Third trimester			13						
Total			32						32

*Includes infants with umbilical hernia and strabismus

†Personal communication

‡Figure supplied by obstetricians of California in answer to a questionnaire that concerned rubella only in the first three months of pregnancy

first two months of the life of the fetus there is an extraordinary vulnerability of certain tissues to the virus of rubella. This is less marked in the third month, with a ratio of 59.5, and in the fourth month, with a ratio of 28.4, and diminishes in the subsequent months of pregnancy.

It has been the custom to discuss these figures according to the trimester of pregnancy. The figures arranged in this manner do not give the startling results of the comparison of the first two months with the last five months because of the relatively small number of normal infants born to mothers who had had rubella in the last trimester. One would expect a much larger number, because in a consideration of the vulnerability of the fetus by trimesters, the ratio of normal babies should increase in inverse proportion to the number born with congenital defects. This is not apparent, and therefore it fails to confirm the startling figures of the first two months in comparison with those of the last five months.

Numerous reports have appeared from the United States and England. It is impossible to do justice to the detailed studies that have been made. With the exception of the survey by Fox and Bortin⁷⁰ in Milwaukee these reports confirm the findings in Australia. Some are simply isolated reports dealing with single cases, whereas others are valuable

as well as by trimesters. From these it is observed that 9 normal babies were found whose mothers had had rubella in the first two months of pregnancy as against 25 in the last five months. But if the entire period of nine months is divided into the three trimesters the figures are 17, 18 and 13 respectively. Here again, there is no inverse ratio of normal children to those with congenital deformities. The addition of Prendergast's⁸⁰ cases is necessary but confusing because the questionnaire sent out to the physicians in California asked only for information regarding babies born to mothers who had suffered rubella in the first trimester. The figures in Table 3, with the exception of the first month with 2 normal babies, lends no support to the figures of congenital deformities, which are strongly indicative of the vulnerability of the fetus in the early months of pregnancy. Indeed, these figures on normal babies tend to sustain the results obtained by Fox and Bortin.⁷⁰ If it is considered, however, that in the past five years there have been reports of only 52 normal babies born of women who had contracted rubella during pregnancy and that only 2 cases have been reported in which the mother had rubella in the first month of pregnancy, the negative evidence supplied in Table 3 and in the survey of Fox and Bortin fades before the overwhelming evidence against rubella. Especially is

cataracts, but 13 showed cardiac lesions with murmurs, precordial bulging and, on x-ray examination, left ventricular dilatations. In 1 case the ductus arteriosus was successfully ligated by operation.

A survey made by Gregg and his co-workers⁷⁵ revealed that the reported cases of rubella in school children in New South Wales from 1933 to 1943 showed a substantial rise to 1000 cases in 1936 and to 4683 in 1937. There was a sharp rise to 30,228 cases in 1940, and during that year 116

TABLE 2 *Relation between Stage of Pregnancy at Onset of Rubella and Birth of Defective and Normal Children (Based on Australian Survey^{68, 72, 75})*

STAGE OF PREGNANCY		INFANTS WITH CONGENITAL DEFECTS	NORMAL CHILDREN	TOTAL
mo				
0 to 1		30	2	32
1 to 2		88	2	90
	First 2 months	—	—	—
2 to 3		59	118	4
	First trimester	—	5	64
3 to 4		28	177	9
4 to 5		3	4	32
5 to 6		2	5	8
	Second trimester	—	7	9
6 to 7		—	33	16
7 to 8		1	4	4
8 to 9		—	2	3
	Last 5 months	—	2	2
	Third trimester	—	6	—
Totals		211	33	244

women were known to have contracted rubella in pregnancy, although the actual number is unknown. To these 116 women 117 babies were born, of whom 78 showed deaf mutism, 15 deaf mutism and heart disease, 4 eye disease, 4 eye and heart disease, 4 heart disease, and 6 deaf mutism and eye and heart disease. All these defects occurred in infants whose mothers had contracted rubella in the first four months of pregnancy, except for 8 cases in which the time of the attack was undetermined. The great majority of the defects occurred in cases in which the attacks had occurred in the first three months. In 1940 only 5 normal babies were found whose mothers had had rubella in pregnancy. The rubella occurred in the third month in 1 case, the fourth month in 1, the fifth month in 2 and the seventh month in 1. Two of the 116 mothers gave a history of an attack of rubella previous to the one in pregnancy. In addition, 20 cases from other years were included in this report, giving a total of 136 cases.

It will be observed that these Australian investigators have delved into the subject from many different angles. The question was raised whether this Australian epidemic was due to some mixed infection. A severe sore throat had been prevalent in Australia, but Swan and his associates⁷² showed that cultures yielded a predominance of *Haemophilus influenzae*. Furthermore, no correlation between the sore throats and the congenital defects could be

established. Thus, a mixed infection with symbiosis was eliminated. Next, the possibility of an unusual strain of rubella virus was considered. It must be kept in mind that this epidemic of 1940 took place during a war year, with troop mobilization in progress. It is well known that many diseases show acceleration in morbidity during military mobilization, and with such acceleration the virulence of the etiologic agent is often increased. Several of these authors remarked on the severity of the rubella attacks and the frequency of rheumatic sequelae. Nevertheless, the incidence and severity of the congenital deformities bore no relation to the severity of the attacks in the mother. Furthermore, reports from England²⁴ and the British Expeditionary Forces²⁷ described epidemic rubella with characteristics of similar severity at the same time. A survey made by Prendergast⁸⁰ of congenital deformities following maternal rubella in California yielded results similar to those reported from Australia, and it was suggested that the Australian strain had been introduced into California because of the close communication between the west coast of America and Australia during the previous five years. It appears that here again an accelerated morbidity due to intensive military mobilization was involved, during which an increased number of pregnant women contracted rubella early in pregnancy, as a result, 40 infants were found to have gross congenital deformities as against 4 normal babies whose mothers had contracted rubella in the first trimester of pregnancy. There seems to be no valid reason for supposing that the virus of rubella during epidemic conditions acquires any augmented powers of invading the fetus in utero. Epidemics merely offer the virus an increased opportunity to attack pregnant mothers. The Australian epidemic was of sufficient proportions to lead Gregg to his discovery of the causal relation of rubella to the congenital cataracts that came under his care.

The various reports from Australia come from independent investigations and surveys. Some of the investigations conducted by specialists deal with cases studied in the surveys. The work of Carruthers⁷⁷ on deafness was carried out on the cases covered in Gregg's⁷⁵ survey, and the actual number of cases with deafness was found to be greater than that in the survey. It is impossible, however, to include these additions in the survey figures. On the other hand, the studies of Evans⁷⁶ on the dental defects of the patient in the survey of Swan et al.⁷² can be incorporated under the survey without reduplication in the number of defects found in this group.

Each author or group of authors have studied the subject either from the point of view of a survey or according to the specialty of the author. There has been a decided lack of any attempt to unify the results. Table 2 presents the figures of

the various surveys of Swan, Gregg and their many associates. This compilation deals with the relation of the time of contraction of rubella during pregnancy and the birth of defective and normal children. It will be seen that in general this conforms with Table 1. The results are startling. When rubella occurred in the first two months of pregnancy there were 118 infants with congenital defects and only 4 normal ones, whereas when the attack of rubella took place in the last five months of pregnancy there were 6 babies with congenital defects and 20 normal ones. This indicates that during the

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	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	
Swan et al. ⁷²			4	2	2	2		1	2	18
Swan et al. ⁷³					1	1				2
Swan et al. ⁷⁴		1		1		1				3
Swan et al. ⁷⁵	1	1						1		4
Gregg et al. ⁷⁶	1		1	1	2		1			6
Fox and Bortin ⁷⁰		4	3	1			1		1	10
Councilman†								1		1
Conte et al. ⁷¹								1		1
Aycock and Ingalls ⁷⁷		1		1					1	3
Totals	2	7	8	6	5	7	5	4	4	48
Prendergast ⁸⁰ *			4							
First trimester			17							
Second trimester			18	21						
Third trimester			15							
Total			52							

*Includes infants with umbilical hernia and strabismus
†Personal communication
‡Figure supplied by obstetricians of California in answer to a questionnaire that concerned rubella only in the first three months of pregnancy

first two months of the life of the fetus there is an extraordinary vulnerability of certain tissues to the virus of rubella. This is less marked in the third month, with a ratio of 59.5, and in the fourth month, with a ratio of 28.4, and diminishes in the subsequent months of pregnancy.

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this apparent when the combined figures assembled from the literature of Australia, the United States and England yield reports of 521 children born with serious congenital deformities during the past five years following maternal rubella. This is a ratio of ten grossly deformed children to one normal child, irrespective of the month in which rubella was contracted.

The details regarding these 521 congenitally deformed children are presented in Table 4. It will be seen that 359 of the cases occurred in Aus-

this has already been emphasized. I have left out several other deformities noted occasionally, such as an arachnodactyly, which is clearly hereditary, and cleft palate, which can be brought about by environmental modifications as well as by genetic mutations.⁸² There were 3 cases of pyloric stenosis, 2 of obliteration of the bile ducts, and 1 of spina bifida. These were all found in conjunction with the other deformities characteristic of infants born of mothers who have had rubella. That there were 3 cases of pyloric stenosis is of significance because

TABLE 4 Severe Congenital Deformities among Children following Rubella in Pregnancy

PLACE	YEAR OF PUBLICATION	AUTHOR	TOTAL NO OF CASES	EYE DEFECTS	DEAFNESS	HEART LESIONS	MICRO CEPHALUS	MENTAL RETARDATION	DENTAL DEFECTS	PYLORIC STENOSIS
Australia	1941	Gregg ¹	78*	78		44				
Australia	1945	Gregg et al. ⁷¹	136	23	85	38	44			
Australia	1943	Swan et al. ⁷²	31	14	7	17	3			
Australia	1944	Swan et al. ⁷³	12	2	5	4				
Australia	1946	Swan and Tostevin ⁶⁸	36	1	22	19	18			2
Australia	1946	Swan et al. ⁷⁴	12	1	6	8		1		
Australia	1944	Evans ⁷⁵							18	
Australia	1945	Vickery ⁷⁶	20	2	20	13				
Australia	1945	Welch ⁷⁷	34		34					
New York	1944	Reese ⁷⁸	3	3		1				
Pasadena, California	1944	Erickson ⁷⁹	11	11		9		2		
Washington, D. C.	1944	Rones ⁸⁰	3	3						
New York	1945	Perera ⁸¹	1	1		1				
Milwaukee, Wisconsin	1945	Greenthal ⁸²	2	1	1	1		1		
Spokane, Washington	1945	de Roeth and Greene ⁸³	2	2		1	1			
Los Angeles	1945	Albaugh ⁸⁴	9	8		8	5			1
Minneapolis	1945	Adams ⁸⁵	2	2		2				
Nashville, Tennessee	1945	Conte et al. ⁸⁶	5	4		4	1	4		
New York	1945	Altman and Dingmann ⁸⁷	1	1	1					
Chicago	1945	Krause ⁸⁸	5	5	1	3		3		
California	1946	Prendergast ^{89†}	40†	40		27		3		
Colorado	1945	Long and Danielson ⁹⁰	6†	6		6				
Richmond, Virginia	1946	Guerry ⁹¹	2	2		1		1		
Houston, Texas	1946	Goar and Potts ⁹²	6	6		5		2		
Massachusetts	1946	Aycock and Ingalls ⁹³	1					1		
Massachusetts	1946	Hopkins ⁹⁴	11	2	11	3		6		
England	1944	Simpson ⁹⁵	2	2		2				
England	1945	Hughes ⁹⁶	1	1	1	1	1			
England	1945	Martin ⁹⁷	30†		30	3				
England	1947	Clayton-Jones ⁹⁸	19†		19		1		2	
Totals			521	221	243	221	74	24	20	3

*In 10 of these cases the diagnosis was suspected but not definitely established.

Since the studies of Carruthers on deaf mutes were done in cases included in the series of Gregg¹ and the Evans studies on dental defects were done in the series of Swan et al.,⁷² which are summarized in the text, these reports are omitted.

†Most conservative use of figures given in order to avoid reduplication in reports of 80 cases from the State.

‡Diagnosis of rubella probable in 6 cases. Total number of probable diagnoses in this table is 22. Cases given as possible diagnoses have been omitted.

tralia, 110 in the United States and 52 in England. The further details are incomplete because many of the patients were examined by specialists in their respective fields,—for example, for eye or ear defects alone,—and some of these infants did not live long enough to reveal deafness, mental retardation or dental deformities. Among these children there were 221 with eye defects, 243 with deafness, 221 with heart lesions, 74 with microcephalus, 24 with mental retardation, and 20 with gross dental deformities. Actually, mental retardation was far more frequent than these figures indicate, since in numerous reports the statement is made that in "many" or "most" of the cases this defect was apparent. Often this was difficult to ascertain because of the existence of deafness or blindness, or both. Furthermore, it is futile to attempt to show the combination of these deformities, since

the finding of these defects among the 521 cases constitutes a high incidence.

It is interesting to note that in the survey made in Tennessee by Conte, McCammon and Christie⁸⁶ it was estimated that the rate of babies with congenital anomalies born of mothers who had had rubella in pregnancy was ten times greater than that for congenitally deformed babies in the population at large.

The finding of these congenital deformities following maternal rubella has naturally aroused interest in the possibility that other infectious diseases, particularly those of virus origin, will cause similar defects. In this respect the Australian investigators, Gregg and Swan with their respective associates, have shown particular interest. Deaf mutism, patent ductus arteriosus, microcephalus and pyloric stenosis have been recorded following

such diseases as measles,^{72 55} mumps, chicken pox and herpes zoster^{68 72} and influenza^{72 95} There is nothing as yet in the literature, however, to suggest that such diseases — with the possible exception of influenza⁷⁴ — compare with rubella in bringing about these congenital deformities, much less a syndrome of eye, ear and heart defects It is important to remember that these deformities may occur without any history of rubella Fox and Bortin⁷⁰ described a woman who in 1937, after a supposedly uneventful pregnancy, gave birth to an infant with bilateral cataracts, in 1945 she is said to have had rubella in the second month of pregnancy, after which she gave birth to a normal infant From my hospital experience I am aware of so many cases erroneously diagnosed as rubella that I cannot be too sure of the accuracy of the state reports on this disease The environmental influence of other infections on the fetus in utero needs the same concerted investigation that is being given to rubella

It must be kept in mind that these reports and surveys represent a backward approach to the problem As such, there is much that is unsatisfactory from an investigative point of view Although rubella is a reportable disease, it is often not reported, and as I have intimated above, it is frequently improperly diagnosed Any backward approach through cases reported to boards of health must take into consideration these possible errors of omission and commission Eventually, we shall have a series of pregnant mothers who have unquestionable rubella and are followed through, the incidence of miscarriages, stillbirths and the findings at autopsy, as well as of normal children and those born with congenital defects, along with the full details of such defects, being given Similar investigations must also be undertaken through the entire field of infectious diseases so that the position of rubella in this respect can be properly ascertained Until adequate studies have been carried out in this manner opinion must be based on such evidence as can be gathered by this backward method of surveys of rubella and of congenitally deformed children

To date the available evidence points to a 10 1 chance (521:52) that a woman who has rubella in pregnancy will give birth to a child with a gross congenital deformity, such as cataracts, deaf mutism, patent ductus arteriosus or mental retardation, and not infrequently with a combination of these defects The incidence of the deformities is in inverse proportion to the month of pregnancy in which the attack of rubella takes place Thus, the likelihood that such a deformity will follow rubella in the first and second months is the greatest It was first estimated at 100 per cent by Australian authors (Table 1) Later this was modified to 118 to 4 by our compilation of Australian surveys (Table 2) Utilizing the figures on normal babies (Table 3) alone, I should lower the estimate still more, but the mass of evidence points to a serious and startling

proportion of deformities — well above 10 1 This ratio changes with each month of pregnancy, and the danger of giving birth to a deformed child decreases to the zero point in the last month (Table 2) In the California survey of the first trimester only, the most conservative estimate was 40 deformed and 4 normal babies⁵⁰ From the Tennessee survey it was estimated by a rather roundabout method that the proportion of deformed children born to mothers who had rubella is ten times greater than the congenitally deformed children born of the population at large⁵¹

Against all this mass of testimony are the results of the survey made in Milwaukee by Fox and Bortin⁷⁰ This report deals with 12 babies born of mothers who had rubella during pregnancy, in 8 of whom the attack of rubella had occurred in the first three months Seven normal babies were born, including a pair of twins There was one stillbirth at the eighth month, and one "blue baby" with hydrocephalus, who subsequently became normal Of course these results differ from those in all the other surveys On careful analysis, however, one cannot agree with the conclusions of these authors, which imply that rubella presents no serious danger to the fetus Two of the children came very near to being badly deformed One died in utero late in pregnancy as stillbirth with hydrocephalus Had it lived the child would in all probability have been a mental defective The other was a "blue baby" with hydrocephalus who subsequently recovered and became "perfectly normal" There were, therefore, two very fortunate escapes among these 8 children, and this signifies a serious hazard in those 2 If the 6 cases in which rubella occurred in the first two months of pregnancy are considered, it might be stated that 2 of the 6 children barely escaped becoming seriously deformed These normal infants studied by Fox and Bortin are included in Table 3 to give the figure of 52 normal babies as a balance against the collected 521 grossly deformed children, giving a ratio for all months of pregnancy of one normal child against ten grossly deformed children — a formidable indictment against rubella and one deserving of special consideration under the treatment of this disease Added to this is the conspicuous demonstration that most of the deformities followed an attack of rubella in the early months of pregnancy Consequently, there appears to be little room for doubt regarding the serious danger of this disease to the fetus during the early months of gestation The evidence at hand, although unsatisfactory in several ways, is sufficient to warrant consideration in the management of this problem

CONGENITAL DEFORMITIES FOLLOWING ATTACKS OF RUBELLA BEFORE CONCEPTION

A curious phenomenon that has come to light is difficult to explain in a disease of such short duration as rubella Hall⁷⁹ reports the case of a child

born in 1942 with a congenital heart lesion, bilateral cataracts and complete deaf mutism, whose mother is said to have suffered a "sharp attack" of rubella six weeks before conception. Sweet¹⁰⁰ supplies the report of a woman who contracted rubella ten days before conception, the date of conception being fixed by the husband's three-day military leave. This pregnancy resulted in the birth of an infant that had bilateral cataracts, patent ductus arteriosus and hydrocephalus and lived only three months. The mother has since given birth to a perfectly normal child. In contrast are the 2 cases reported by Swan and Tostevin⁶⁸ in which rubella was contracted thirteen days and six days, respectively, before conception. This was figured out on the assumption that "ovulation occurs approximately fourteen days before the onset of the next menstrual cycle and that fertilization takes place within twenty-four to forty-eight hours of ovulation." It is interesting that in the first case a therapeutic abortion was carried out in view of the possibility that the child would be malformed. The specimen sent to the pathological laboratory consisted of fragments of tissue. Both eyes were intact, and further histopathological examination revealed no abnormality. The other patient went to term, and the child was normal.

TREATMENT

Aside from the problem of rubella in pregnancy, this disease is so relatively mild in the vast majority of cases that the natural recuperative powers of the body need no special help from the armamentarium of the physician. If fever is present bed rest appears to be indicated, unless the new notion of getting sick people out of bed captures the fancy of the modern doctor. Certainly, bed rest need not be enforced too strictly. One has but to be reminded that in another virus disease — namely, mumps — it has been clearly shown that the old notion of strict bed rest does not diminish the incidence of orchitis. It is highly improbable that complete rest in bed will diminish the rare complications of rubella. Most of the patients with mild cases do not stay in bed anyway and do perfectly well if they are permitted to be up and about. I had the opportunity of observing an epidemic of rubella in a regiment in a training area. The first 2 patients were admitted to a measles ward. After this affront, with the connivance of two superior officers, the subsequent patients remained on full duty. Those who were sick remained in quarters. The epidemic burned itself out without any sequelae other than a threatened court martial, which never materialized. This method of dealing with epidemics of rubella has been successfully carried out in lay institutions. During the Blitz in London, sadly needed beds for casualties were occupied by patients with rubella.

In 1814, when blood letting was in vogue, Maton⁶ gave due consideration to this form of therapy,

deeming it unnecessary in cases of rubella. He advocated nothing more than purgation. Paterson,⁷ in 1840, favored the fad of his day, recommending the application of leeches to the chin and sternum, as well as enough wine of colchicum to induce vomiting and purging. If constipation is present it needs gentle correction. A reasonable amount of activity of the skeletal muscles tends to avoid this condition and is preferable to overactivity of the smooth muscles of the entire gastrointestinal tract. If the eruption is accompanied by itching, which is rare, calamine lotion is indicated. Some physicians have found warm baths helpful. A little activity takes the mind off this minor disturbance. A good night's sleep can be achieved in a quiet environment without the aid of a narcotic. Gargles and nose drops are quite unnecessary.

It goes without saying that sulfonamides and penicillin are not indicated, and yet I have seen both generously applied, according to the spirit of the times, before the patient was admitted to the hospital. This is a pure waste of valuable medicines. The same thing could be said of the vitamins, there appears to be ample vitamin reserve to carry a patient through an attack of this disease. As a matter of fact, no one has the slightest idea of the relation of vitamins to resistance to rubella. Serum therapy is quite unnecessary for the ordinary case. Jacob Bigelow's¹⁰¹ address, "On Self-Limited Diseases," delivered before the Massachusetts Medical Society in 1835, is still good prescribed reading. In short, there is little that need be done except to make the patient comfortable, and since in the vast majority of cases the patient suffers not so much from discomfort as from the deprivation of his usual pursuits and activities, the possible advantages and disadvantages of imposing restrictions should be carefully considered. Before the recognition of the deleterious effects of rubella on the fetus in utero there was a growing tendency in various boards of health to remove all isolation requirements. In view of the newer knowledge of this disease this idea needs reconsideration. The treatment of the pregnant woman who suffers an attack of rubella is discussed below.

PREVENTION

Protection against rubella is like protection against an atom bomb, and can be summed up in one word — distance. If exposure could be avoided, the disease itself could, of course, be prevented. On the other hand, exposure to the disease in childhood appears to be advantageous, since an attack is likely to afford a lifelong immunity. Therefore, the proposition that it is advisable to have rubella in childhood advances the corollary that it is advisable for all children to be thoroughly exposed, which means the removal of all isolation precautions, so that as many children as possible can have the disease and thereby acquire immunity from sub-

sequent attacks. The fallacy in such a sweeping statement lies in the fact that many children in the community have mothers who are pregnant and who may or may not have had rubella — many mothers are ignorant of whether or not they have had it. It has already been pointed out that the immunity from one attack is not always permanent, it is only relatively permanent. Thus, the removal of precautionary isolation may entail the danger of rubella in pregnant mothers contracted from children exposed in kindergarten or school. Certainly, this contingency is to be avoided if possible, but it presents one of the most difficult problems. It is easy enough to say that all children should be inoculated with the virus of rubella, but an active virus would give rise to the disease itself, which would be communicable to others. Therefore, although it is safe to say that an epidemic of rubella should be allowed to run its course in asylums and boarding schools and in such colleges as can be isolated for the time being, the same statement cannot be postulated for day nurseries, kindergartens and day schools or colleges situated in metropolitan centers.

It has been pointed out above that this disease appears to be communicable just prior to the eruption and that communicability diminishes abruptly with the disappearance of the rash. Consequently, since the rash is of short duration, isolation for the eruptive period is effective for only about half the period of infectivity. Thus, the factor of time must also be considered in relation to distance in the matter of exposure.

Barenberg and his co-workers¹⁰² have offered presumptive evidence that the intramuscular injection of pooled serum or plasma will prevent rubella in children. The duration of such protection is unknown. This method could be utilized in children exposed to rubella whose mothers are pregnant. At the same time, larger doses could also be injected into the pregnant mothers. Just how reliable such an attempt at affording passive immunity would be in the event of a protracted epidemic, even though repeated doses were given, remains to be determined. One must take into consideration the possibility that such a serum will be contaminated with infectious hepatitis. Gamma globulin, which has been proved to be effective after exposure to measles and ineffective after exposure to chicken pox, is as yet an untried weapon against rubella. Until a vaccine of modified rubella virus that will not give rise to a communicable form of the disease and yet will afford a permanent immunity has been perfected, the complicated problem of protecting pregnant mothers from contracting rubella will remain.

TREATMENT OF THE PREGNANT MOTHER WHO CONTRACTS RUBELLA

It would be interesting to know whether pregnancy renders a woman more susceptible to rubella.

Apparently, the manifestations of rubella in the pregnant woman are no severer than those in other persons, thus, there is no real direct danger from the virus to the mother herself. Once exposure has taken place and the incubation period has passed and the rubella eruption has reached the stage where the disease can be recognized, there is the possibility — in the early weeks of pregnancy, the probability — that the virus has gained access to the fetus. Evidence has been presented pointing to the susceptibility, which is particularly marked in the first two months of life, of certain fetal tissues to the virus of rubella. This premise presupposes that the virus would attack the fetal tissues as soon as it became active in the mother, if not sooner. If the virus has already combined with these fetal structures the question arises whether any number of protective antibodies contained in antisera administered to the mother would preclude serious damage to the fetus. By the time the disease is recognizable in the mother it is highly probable that the virus would already have accomplished serious injury to the more susceptible embryonic tissues, and that no amount of antiserum could offset the damage. The administration of such an antiserum in any of its present forms would leave one with the uncertainty of its efficacy.

Threatened Miscarriage

Whether or not antiserum has been administered, any signs of miscarriage ought to be welcomed, and I can see no justifiable reason for any attempts to avoid such a favorable event. There is nothing in the dictates of the medical profession or in the common law of English-speaking countries that instructs a physician to attempt to prevent a miscarriage in the face of the evidence that has been presented. To bring up the religious motive of preserving life at all costs is on a par with the superstition of the Hindu who will not kill a cobra that attacks his own child because the cobra is a sacred animal.

Of course, a human life is sacred. Yet, under certain circumstances, one may take a human life in self-defense, both in peace and in war. A nation at war expends the lives of its citizens. Physicians are not bound to preserve life at all costs. Nothing is gained by saving a life when agony and anguish lie ahead, whether in the death throes of cancer or in the future birth of a grossly deformed infant. Because human life is sacred, there are exceptions to preserving it at all costs and under all circumstances. Physicians are now faced with a new exception. No attempt should be made to prevent a threatened miscarriage in the course of or after an attack of rubella, especially when the disease occurs in the early months. It is entirely up to the judgment of the attending physician to bring this to completion by surgical means. The medical profession is engaged in the prevention of disease, the preservation

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of life and the amelioration of suffering. The immediate problem does not come under the much discussed topic of legalizing euthanasia, which has to do with that praiseworthy function of making impending death comfortable. The problem presented by rubella in pregnancy deals with the prevention of suffering in its broadest sense.

Therapeutic Abortion and Its Medicolegal Aspects

The instigation of a therapeutic abortion is quite a different matter from allowing a threatened miscarriage to proceed and bringing it to completion by surgical means. The suggestion of terminating pregnancy after an attack of rubella was first introduced by Swan and his associates.⁷² In a subsequent article it was made clear that no legal grounds existed in Australia for the termination of pregnancy after rubella.⁷³ Furthermore, they gave as their expressed opinion that legislation to such an end might lead to its abuse. Albaugh⁶⁹ and Lynch,¹⁰³ in America, and Hughes,⁹⁶ in England, have urged that caution be used in the consideration of abortion. Fox and Bortin⁷⁰ found in the results of their Milwaukee investigations no justification for considering the termination of pregnancy. When one contemplates the mass of cumulated factual evidence presented in this paper the idea of therapeutic abortion cannot be pushed aside. Such abortions in 3 cases have already been reported in the medical literature.⁷⁴⁻¹⁰¹

In dealing with a diseased patient the physician uses every effort to remove all obstacles in the way of recovery. The word "recovery" must be construed to include the aftereffects of the disease. If a woman suffers an attack of rubella during the first months of pregnancy, the chances of her giving birth to a grossly deformed child are sufficient to warrant an abortion from the purely medical point of view to ensure complete recovery from the aftereffects of the disease. The law forbids physicians to perform an operation for that purpose.

According to the common law and the statutes in some states, it is illegal to terminate pregnancy except to save the life of the mother. For instance, therapeutic abortion is permitted in the case of a pregnant woman suffering from tuberculosis. This is done for the safety of the expectant mother. The consultation of a second physician—and usually the permission of the executive committee of the hospital—is required. After an attack of rubella the life of the mother is usually not endangered by a grossly deformed living fetus, only if the fetus develops a massive hydrocephalus can the life of the mother be said to be threatened. This is a relatively minimal danger. Nevertheless, such a possibility exists, even though remote, and could be seized on as a point in law, and possibilities are being dealt with. The woman with tuberculosis does not always succumb from carrying a child, but she is likely to do so. An attack of rubella in the early

months of pregnancy does not always result in serious malformations in the fetus, but it may do so. Such a possibility weighs heavily on the minds of the attending physician and the parents.

The purpose of terminating pregnancy is to prevent the birth of a deformed infant and to allow the mother to conceive again under more auspicious circumstances. The desire to accomplish this is irrelevant in the eyes of the law. From the legal point of view this desire is prompted by social reasons, which are not acceptable as valid grounds for abortion. These grounds are actually far more valid than the grounds in which abortion is usually sought, because the birth of a deformed child acts as a deterrent to future pregnancies. The birth of a deformed child as a result of rubella in no way prevents the future birth of normal babies. Nevertheless, in Australia, investigations showed that mothers of infants deformed by rubella refrained from having more children because of the fear of giving birth to another defective child or because the care of the defective child precluded their having any more children.⁷⁴

If the fetus dies the uterus may be emptied. There is no question here of destroying life. Consequently, the determination of a dead fetus warrants emptying of the uterus. It can always be argued that the presence of a macerated fetus could serve as a nidus for the Welch bacillus, so frequently inhabiting the intestinal tract of normal persons. Such a possibility, however, is remote. Ordinarily, a dead fetus offers no particular danger to the mother. The real question is how to determine the presence of a dead fetus in the early months of pregnancy. Failure of the uterus to grow is, of course, an indication that the fetus is dead. Consequently, if the attending obstetrician decides that the fetus is not living, he may empty the uterus. A consultation is indicated, to share responsibility, and the written permission of the expectant mother, as well as of the husband, should be obtained. Although the common law permits emptying of the uterus when the fetus is dead, the statutes on this whole subject vary in different states—for example, in Massachusetts, Maine, New York and Iowa.

The fundamental law regarding abortion lies in the Offense against the Persons Act of England. Any approach to this law as it relates to the pregnant woman who suffers an attack of rubella must be made with two possibilities in mind. The first, which has to do with a favorable interpretation of this law and the statutes that pertain to it, would permit an exception under these circumstances. The second, which concerns a change in the statutes, would grant permission to carry out abortion under the explicit circumstance of an attack of rubella. It is my purpose to show that a favorable interpretation has been rendered in relation to this subject in a court of law, and to bring out a pertinent bit of history regarding a law that was entirely changed.

The present status of the law regarding abortion in reference to rubella has been reviewed in an editorial in the *Lancet*. It is pointed out that abortion is a statutory felony under the Offense against the Persons Act. A later proviso was introduced as an amendment whereby no person should be guilty under this section if the act "was done in good faith for the purpose only of preserving the life of the mother." In 1938 Mr Justice Macnaghten, in charging a jury, suggested that this clause did not mean that the surgeon operates only if the life of the mother is in immediate danger. It was his opinion that this section of the law construed "reasonably" would protect the surgeon if in his best judgment the continuation of pregnancy would have led to the patient's becoming "a physical and mental wreck." The editorial continues as follows: "If a woman can be assured that her child is certain to be born with some terrible deficiency, it might well have the same effect." Actually, there is no more assurance that the child will be born with gross deformities as the result of rubella than there is that the woman with tuberculosis will die if allowed to continue her pregnancy. Nevertheless, if a woman is aware of the statistical evidence in her particular case regarding the period in her pregnancy when the attack of rubella took place, there can be no doubt that she would become "a mental and physical wreck" if the pregnancy were allowed to continue. Indeed, it could be said that in the end it might endanger her health as much as an attack of tuberculosis. Justice Macnaghten's opinion was rendered before anything was known of the dangers of rubella during pregnancy. A liberal interpretation of the law based on his construction would depend on the court and the sympathy of the jury. A closer interpretation of the law would stress the fact that the mother's life was not endangered by the attack of rubella, and that the surgical termination of pregnancy under such circumstances is therefore a felony. It is necessary to point out that conviction of such a felony brings a severe penalty, with fine, imprisonment and the loss of license to practice.

It was pointed out above that congenital deformities were at one time attributed to a witch casting a spell on a pregnant woman. Witchcraft was generally believed in, and there were laws regarding it. Those suspected were imprisoned, brought to trial and, on conviction, put to death. "Thou shalt not suffer a witch to live" (*Exodus 22:18*) is one of the laws of Moses. Jews, Roman Catholics and Protestants tortured, drowned, hanged and burned those suspected of practicing witchcraft.

Two hundred and fifty years ago the Salem witch trials rocked New England. The Scriptures were quoted by Puritan clergymen in support of these trials just as some clergymen today quote them as an argument against euthanasia. The presiding judge showed no mercy. Two physicians sat on the jury and contributed to the torture of the victims

by their cruel tests.¹⁰⁶ Those convicted were hanged. This went on for a year. The turning point came when the citizens of Boston pointed the finger of suspicion at the wife of the Royal Governor. Witchcraft was threatening those on high. The Governor now listened to the more enlightened members of the community. Clergymen, physicians, lawyers and merchants denounced these proceedings as cruel and barbarous, and the witch hunts came to a halt. A wave of repentance swept the populace, and prayers for forgiveness were offered in the churches. Horrible as it all was, the relative abruptness with which the trials stopped and the open repentance of the populace were unique in history. These New Englanders saw to it that this Mosaic law should never again occasion such injustice.

Forty-five years later the following law¹⁰⁷ enacted in the reign of James I was repealed in England:

All persons invoking any evil spirit, or consulting, covenanting with, entertaining, employing, feeding, or rewarding any evil spirit to be used in any witchcraft, sorcery, charm, or enchantment should be guilty of felony without benefit of clergy, and suffer death.

A new law prescribed that "No prosecution shall for the future be carried on against any person for conjuration, witchcraft, sorcery, or enchantment."¹⁰⁷

The last witch was burned in Spain in 1791 and in Poland in 1793 — a hundred years after the Salem trials.¹⁰⁸ The following quotation from a great scholar on witchcraft is instructive: "No jury, whether in a witch-trial or in any other case, can be more enlightened than the general run of the vicinage."¹⁰⁸ It has been estimated that in England thirty thousand persons suffered death from suspicion of witchcraft during a hundred and fifty years. By rough calculation based on the reports of the last five years there could have been at least an equal number of seriously deformed children born of mothers who had rubella in pregnancy during the past hundred and fifty years in English-speaking countries. New England has shown that, as soon as public opinion becomes sufficiently aroused, it can do away with laws that prove to be unjust. It is to be hoped that in this day and age a change in laws regarding abortion will not have to wait for the virus of rubella to attack the wives of our lawmakers.

Gregg's discovery that rubella early in pregnancy offers great danger of gross deformities in the child represents a distinct advance in medical knowledge. English-speaking countries can take pride in the many painstaking investigations that have enlarged the knowledge on this subject. The cumulated factual evidence presents a challenge to the existing law relative to therapeutic abortion. Although further investigations are needed to determine the accuracy of the evidence, it is certainly sufficient to warrant consideration of another amendment to grant permission for surgical interference after an attack of rubella. Such an amendment can be achieved only through enlightened public opinion.

The argument that the amendment to the law might be abused is, to use the words of the lawyers, "irrelevant, incompetent and immaterial," if untold mental suffering is thereby avoided and more births of healthy infants are achieved

REFERENCES

- 65 Symposium on congenital factors in disease *Brit M Bull* 4 165-214, 1946
- 66 Hale, F Relation of vitamin A to anophthalmos in pigs *Am J Ophth* 18 1087-1093, 1935
- 67 Warkany, J, and Schraffenberger E Congenital malformations of eyes induced with maternal deficiency of vitamin A *Am J Dis Child* 69 330, 1945
- 68 Swan, C, and Tostevin, A L Congenital abnormalities in infants following infectious diseases during pregnancy, with special reference to rubella third series of cases *M J Australia* 1 645-659, 1946
- 69 Goar E L, and Potts, C R Relationship of rubella in mother to congenital cataracts in child *Am J Ophth* 29 566-569 1946
- 70 Fox, M J, and Bortin, M M Rubella in pregnancy causing malformations in newborn *J A M A* 130 568, 1946
- 71 Ramli, A H and Hayward O S Unpublished data
- 72 Swan, C, Tostevin, A L, Moore B, Mayo H, and Black, G H B Congenital defects in infants following infectious diseases during pregnancy, with special reference to relationship between German measles and cataract deaf-mutism, heart disease and microcephaly and to period of pregnancy in which occurrence of rubella is followed by congenital abnormalities *M J Australia* 2 201-210, 1943
- 73 Swan C, Tostevin, A L, Mayo, H, and Black, G H B Further observations on congenital defects in infants following infectious diseases during pregnancy, with special reference to rubella *M J Australia* 1 409-413, 1944
- 74 Swan, C, Tostevin, A L, and Black G H B Final observations on congenital defects in infants following infectious diseases during pregnancy with special reference to rubella *M J Australia* 1 889-908, 1946
- 75 Gregg, N M, Beavis, W R, Heseltine M, Machin, A E Vickery D, and Meyers, E Occurrence of congenital defects in children following maternal rubella during pregnancy *M J Australia* 2 122-126 1945
- 76 Evans M W Congenital dental defects in infants subsequent to maternal rubella during pregnancy *M J Australia* 2 225-228 1944
- 77 Carruthers, D G Congenital deaf mutism as sequela of rubella-like maternal infection during pregnancy *M J Australia* 1 315-320 1945
- 78 Welch L St V Rubella and congenital defects *M J Australia* 1 574, 1945
- 79 Vickery, D Congenital defects following maternal rubella *M J Australia* 1 332 1945
- 80 Prendergast J J Congenital cataract and other anomalies following rubella in mother during pregnancy California survey *Arch. Ophth* 35 39-41 1946
- 81 Conte, W R, McCammon C S and Christie A Congenital defects following maternal rubella *Am J Dis Child* 70 301-306, 1945
- 82 Warkany, J, Nelson, R C, and Schraffenberger E Congenital malformations induced in rats by maternal nutritional deficiency cleft palate *Am J Dis Child* 65 882-894 1943
- 83 Reese, A B Congenital cataract and other anomalies following German measles in mother *Am J Ophth* 27 483-487 1944
- 84 Erickson, C A Rubella early in pregnancy causing congenital malformations of eyes and heart. *J Pediat* 25 281 283, 1944
- 85 Rones, B Relationship of German measles occurring during pregnancy to congenital ocular defects *M Ann District of Columbia* 13 285 287, 1944
- 86 Perera, C A Congenital cataract following rubella in mother report of case. *Am J Ophth* 28 186, 1945
- 87 Greenthal, R M Congenital malformations in infant caused by rubella early in pregnancy report of two cases *Arch Pediat* 62 53 56, 1945
- 88 de Roeth, A F M and Greene P B Rubella cataract congenital cataract and other defects following German measles during pregnancy of mother *Northwest Med* 44 222, 1945
- 89 Albaugh C H Congenital anomalies following maternal rubella in early weeks of pregnancy, with special emphasis on congenital cataract *J A M A* 129 719-723 1945
- 90 Adams, F H Rubella in pregnancy and congenital malformations. *Journal Lancet* 65 197, 1945
- 91 Altmann F, and Dingmann, A Congenital deafness and cataract following rubella in mother *Arch Otolaryng* 42 51, 1945
- 92 Krause, A C Congenital cataracts following rubella in pregnancy *Ann Surg* 122 1049-1055 1945
- 93 Long, J C, and Danielson R W Cataracts and other congenital defects in infants following rubella in mother *Arch Ophth* 34 24-27 1945
- 94 Guerry, DuP, III Congenital glaucoma following maternal rubella report of 2 cases *Am J Ophth* 29 190-193 1946
- 95 Hopkins, L A Congenital deafness and other defects following German measles in mother *Am J Dis Child* 72 377 381, 1946
- 96 Hughes I Congenital defects following rubella in pregnancy *Proc Roy Soc Med* 39 17 1945
- 97 Martin, S M Congenital defects and rubella *Brit M J* 1 855, 1945
- 98 Clayton-Jones E Rubella as cause of congenital deafness in England *Lancet* 1 56-61 1947
- 99 Hall M B Deafness from rubella in pregnancy *Brit M J* 1 737, 1946
- 100 Sweet, C Personal communication
- 101 Bigelow J On self limited diseases. In *Modern Inquiries Classical, professional, and miscellaneous* Second edition 375 pp Boston Little Brown & Co 1867 Pp 143 172
- 102 Barenberg L H, Levy W, Greenstein N M, and Greenberg B Prophylactic use of human serum against contagion in pediatric ward further observations with special reference to measles and rubella *Am J Dis Child* 63 1101 1109 1942
- 103 Lynch, F W Discussion of Albaugh "
- 104 Cordes, F C, and Barber A Changes in lens of embryo after rubella microscopic examination of eight week-old embryo *Arch Ophth* 36 135 140 1946
- 105 Medicine and the Law Abortion for probable defects in child *Lancet* 1 208, 1946
- 106 Chandler, P W *American Criminal Trials* Boston Little & Brown, 1841 Pp 67-140
- 107 Osborn, A S *The Problem of Proof* 539 pp Albany New York Boyd Printing Co 1946
- 108 Kittredge, G L *Witchcraft in Old and New England* 640 pp Cambridge Harvard University Press 1929 Pp 370 and 372

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

CASE 33261

PRESENTATION OF CASE

A thirty-year-old man entered the hospital because of convulsive seizures.

He had been well until ten days before admission, when a severe headache had developed. On the next day there was an attack of slight twitching of the right upper lip, shortly afterward the patient became unconscious and had a generalized convulsive seizure. In the next ten hours he had two more attacks, which his wife described as beginning with a twitching of the right corner of the mouth followed rapidly by jerking movements of the right arm and a generalized convulsion. All episodes were preceded by a strange, unpleasant sensation of taste and smell and were followed by transitory nominal aphasia. Three days later the seizures recurred but were limited to the right side of the face and the right arm, without loss of consciousness, and were preceded by an aura of an unpleasant taste and odor. Five days before admission an attack was followed by persistent difficulty in naming objects, clumsiness of the right hand and "numbness" of the right hand and forearm and the right side of the face. The headache recurred intermittently. It was localized to the left temporal region if the patient lay on the left side, but it was severer and more generalized when he lay on the right side. When turning to the left side he felt as though "a bag of water" flowed over to the left side of his head. There had been no visual disturbance, nausea or vomiting.

The past history revealed no serious illnesses. The patient had been in an automobile accident five years previously, with momentary loss of consciousness.

Physical examination revealed a patient who was mentally alert but who had difficulty naming familiar objects. Speech was slurred and hesitant. The visual acuity, visual fields, fundi, pupils and ocular movements were normal. The right hand and arm were weak and clumsy. There was loss of position and gnostic sense in the right hand and a similar

although less marked motor and sensory deficit in the right lower extremity. The tongue deviated to the right. The remaining cranial nerves were normal. The arm, knee and ankle jerks were more active on the right than on the left. No pathologic reflexes were elicited.

The temperature, pulse and respirations were normal. The blood pressure was 135 systolic, 90 diastolic.

Examination of the blood showed a hemoglobin of 15 gm and a white-cell count of 7000. Urinalysis was negative. The initial spinal-fluid pressure was equivalent to 165 mm of water, with 1 lymphocyte per cubic millimeter and a total protein of 45 mg per 100 cc. The gold-sol test was negative. X-ray films of the chest were normal. An electroencephalogram showed a "generally rather ragged record, the raggedness most marked at and around the left parietal region." There were no well defined slow waves or indications of a well defined focus.

During the hospital stay, the patient complained occasionally of headache, which was relieved once by lumbar puncture. On the fifth hospital day he had a convulsive seizure involving the face, arm and leg on the right side. Burr holes were made, and on the following day a ventriculogram was taken. Only a small quantity of air was visible in the right lateral ventricle, which appeared to be displaced toward the right.

An operation was performed on the sixth hospital day.

DIFFERENTIAL DIAGNOSIS

DR JAMES B AYER: Three important points are not mentioned in the record. Was there a previous x-ray examination, and what did the plain film show? There is no note of a blood Wassermann or Hinton test. Was the patient right handed? Are the x-ray films of the later examination available?

DR STANLEY M WYMAN: These films were made after the burr holes.

DR AYER: Can any air be seen?

DR JOST MICHELSEN: This was a difficult ventriculogram. The patient had a seizure during the procedure, and only 8 cc of air could be injected.

DR AYER: Is that air in the area of the lateral ventricles?

DR WYMAN: I cannot be sure.

DR AYER: Assuming that the report is correct, that the right ventricle has some air in it, the left none, and that the right ventricle is displaced somewhat to the right, let us continue with the analysis. The first thing to ask ourselves is whether the patient had a gross anatomic intracranial lesion, because this must have been an intracranial disturbance. I think that we can say that this is so. The reason I ask that question is that once in a while focal convulsions appear in uremia and other conditions without gross pathologic changes. There

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REFERENCES

- 65 Symposium on congenital factors in disease *Brit M Bull* 4 165-214, 1946
- 66 Hale, F Relation of vitamin A to anophthalmos in pigs *Am J Ophth* 18 1087-1093, 1935
- 67 Warkany, J, and Schraffenberger, E Congenital malformations of eyes induced with maternal deficiency of vitamin A. *Am J Dis Child* 69 330 1945
- 68 Swan, C., and Tostevin, A L Congenital abnormalities in infants following infectious diseases during pregnancy, with special reference to rubella third series of cases *M J Australia* 1 645-659, 1946
- 69 Goar, E L, and Potts C R Relationship of rubella in mother to congenital cataracts in child *Am J Ophth* 29 566-569, 1946
- 70 Fox, M J, and Bortin, M M Rubella in pregnancy causing malformations in newborn *J A M A* 130 568, 1946
- 71 Ramli, A H, and Hayward, O S Unpublished data
- 72 Swan, C, Tostevin, A L, Moore, B, Mayo H, and Black G H B Congenital defects in infants following infectious diseases during pregnancy with special reference to relationship between German measles and cataract, deaf-mutism, heart disease and microcephaly and to period of pregnancy in which occurrence of rubella is followed by congenital abnormalities *M J Australia* 2 201-210, 1943
- 73 Swan, C, Tostevin, A L, Mayo, H, and Black, G H B Further observations on congenital defects in infants following infectious diseases during pregnancy, with special reference to rubella *M J Australia* 1 409-413 1944
- 74 Swan, C, Tostevin, A L, and Black G H B Final observations on congenital defects in infants following infectious diseases during pregnancy, with special reference to rubella *M J Australia* 1 889-908 1946
- 75 Gregg, N M, Beavis W R, Heseltine M, Machin, A E, Vickery, D, and Meyers, E Occurrence of congenital defects in children following maternal rubella during pregnancy *M J Australia* 2 122-126, 1945
- 76 Evans, M W Congenital dental defects in infants subsequent to maternal rubella during pregnancy *M J Australia* 2 225-228, 1944
- 77 Carruthers, D G Congenital deaf-mutism as sequela of rubella-like maternal infection during pregnancy *M J Australia* 1 315 320 1945
- 78 Welch, L St V Rubella and congenital defects *M J Australia* 1 574 1945
- 79 Vickery D Congenital defects following maternal rubella *M J Australia* 1 332 1945
- 80 Prendergast J J Congenital cataract and other anomalies following rubella in mother during pregnancy California survey *Arch Ophth* 35 39-41 1946
- 81 Conte W R, McCammon, C S and Christie A Congenital defects following maternal rubella *Am J Dis Child* 70 301-306, 1945
- 82 Warkany, J, Nelson, R. C, and Schraffenberger E Congenital malformations induced in rats by maternal nutritional deficiency cleft palate *Am J Dis Child* 65 882-894 1943
- 83 Reese, A B Congenital cataract and other anomalies following German measles in mother *Am J Ophth* 27 483-487, 1944
- 84 Erickson C A Rubella early in pregnancy causing congenital malformations of eyes and heart *J Pediat* 25 281 283, 1944
- 85 Rones, B Relationship of German measles occurring during pregnancy to congenital ocular defects *M Ann District of Columbia* 13 285 287 1944
- 86 Perera, C A Congenital cataract following rubella in mother-report of case *Am J Ophth* 28 186 1945
- 87 Greenthal, R M Congenital malformations in infant caused by rubella early in pregnancy report of two cases *Arch Pediat* 62 53 56 1945
- 88 de Roeth, A F M, and Greene, P B Rubella cataract congenital cataract and other defects following German measles during pregnancy of mother *Norikwest Med* 44 222, 1945
- 89 Albaugh, C H Congenital anomalies following maternal rubella in early weeks of pregnancy, with special emphasis on congenital cataract *J A M A* 129 719-723, 1945
- 90 Adams, F H Rubella in pregnancy and congenital malformations. *Journal Lancet* 65 197, 1945
- 91 Altmann, F, and Dingmann, A Congenital deafness and cataract following rubella in mother *Arch Otolaryng* 42 51, 1945
- 92 Krause, A C Congenital cataracts following rubella in pregnancy *Ann Surg* 122 1049-1055, 1945
- 93 Long J C, and Danielson R W Cataracts and other congenital defects in infants following rubella in mother *Arch Ophth* 34 24-27 1945
- 94 Guerry, DuP III Congenital glaucoma following maternal rubella report of 2 cases *Am J Ophth* 29 190-193 1946
- 95 Hopkins, L A Congenital deafness and other defects following German measles in mother *Am J Dis Child* 72 377 381 1946
- 96 Hughes I Congenital defects following rubella in pregnancy *Proc Roy Soc Med* 39 17 1945
- 97 Martin, S M Congenital defects and rubella *Brit M J* 1.855, 1945
- 98 Clayton-Jones, E Rubella as cause of congenital deafness in England *Lancet* 1 56-61, 1947
- 99 Hall M B Deafness from rubella in pregnancy *Brit M J* 1 737, 1946
- 100 Sweet, C Personal communication
- 101 Bigelow, J On self limited diseases. In *Modern Inquiries Classical, professional, and miscellaneous* Second edition 375 pp Boston Little Brown & Co 1867 Pp 143 172
- 102 Barenberg L H, Levy, W, Greenstein N M, and Greenberg B Prophylactic use of human serum against contagion in pediatric ward further observations with special reference to measles and rubella *Am J Dis Child* 63 1101 1109 1942
- 103 Lynch, F W Discussion of Albaugh "
- 104 Cordes, F C, and Barber A Changes in lens of embryo after rubella microscopic examination of eight week-old embryo *Arch Ophth* 36 135 140, 1946
- 105 Medicine and the Law Abortion for probable defects in child *Lancet* 1 208 1946
- 106 Chandler, P W *American Criminal Trials* Boston Little & Brown, 1841 Pp 67-140
- 107 Osborn, A S *The Problem of Proof* 539 pp Albany New York Boyd Printing Co, 1946
- 108 Kittredge G L *Witchcraft in Old and New England* 640 pp Cambridge Harvard University Press 1929 Pp 370 and 372

metastases In the case under discussion it failed to do so The evidence, I believe, points to a single lesion I see nothing to suggest a lesion elsewhere in the brain or in the nervous system, and I therefore believe that metastasis of any form is not likely Moreover, the man was only thirty years old, and the usual metastases occur in older people Two fairly common types of brain tumor that are seen in this location are glioma, which may well give exactly these symptoms, and meningioma Between the two there is not much to choose Frequently, meningioma is likely to grow from a petrous ridge or other dural attachment that shows roughening on x-ray study, which is not reported This is negative evidence that meningioma is less likely and suggests the more probable tumor to be glioma I should not care to say which type, but evidently it was rapidly growing and that is as far as I dare go

Could the lesion have been anything else? There is one condition that occurs rarely blocking of the foramen of Monro, leading to unilateral dilatation of the ventricle, which in turn causes tumor-like symptoms In this patient an attempt to inject air into the left ventricle seems to have failed, suggesting that it was not enlarged

I must therefore conclude that we are dealing with an expanding lesion in the left temporoparietal region, not a large one because of the fact that it was not causing an excessive increase in intracranial pressure as judged by the films of the skull, the headache and the spinal-fluid pressure I should favor an infiltrating glioma Certainly, a surgical operation is indicated

DR CHARLES S KUBIK This patient was operated on by Dr Michelsen, who will describe the pathological findings But before he does that, are there any suggestions regarding the diagnosis?

DR JAMES C WHITE The only comment I can make is that we have recently been over our brain tumors during the decade 1935-1944, and out of 640 cases in that period 160 patients had seizures, and in those that had seizures astrocytomas were the highest group — 50 per cent of 88 cases The meningiomas were the second greatest, occurring in 35 per cent The percentage in the Montreal Neurological Institute is even higher, but in considering Penfield's* series one must remember that anyone who has epilepsy in Canada goes to Montreal I therefore believe that his statistics of epilepsy associated with brain tumor are overweighted Two thirds of his patients with supratentorial tumors — and in this hospital, one third — had epilepsy In glioblastoma multiforme the incidence of seizure is 20 per cent and in metastatic carcinoma, 14 per cent In Montreal many patients with astrocytoma and meningioma had epileptic seizures

*Penfield W., and Erickson T C *Epilepsy and Cerebral Localization: A study of the mechanism, treatment and prevention of epileptic seizures* 1937 Springfield Illinois Charles C Thomas 1941

for months or years before operation, in this hospital the duration was only one month It is also of interest to note that convulsions accompanied many of our brain abscesses

CLINICAL DIAGNOSIS

Left frontoparietal brain tumor, probably glioma

DR AYER'S DIAGNOSIS

Expanding lesion, left temporoparietal region, probably glioma

ANATOMICAL DIAGNOSIS

Brain abscess

PATHOLOGICAL DISCUSSION

DR MICHELSEN Our reasoning was very much the same as Dr Ayer's First of all, we were not absolutely certain that we were dealing with an expanding lesion The ventriculogram was done to demonstrate the type of disease Although the filling was rather poor, we were satisfied, because there was definite displacement of the ventricular system The location of the lesion was quite obvious clinically The preoperative diagnosis was brain tumor We expected a glioma, and because of the rapid course of the disease we thought that this would probably be a glioblastoma multiforme A bone flap was turned down in the usual fashion A lesion was readily discovered on the surface, involving the lower portions of the anterior and posterior central gyri When we began to take a biopsy, pus escaped from a small opening On spreading the cortex, a typical abscess wall was found The pus contained an alpha-hemolytic streptococcus All of it was evacuated The dura was closed around the abscess A catheter drain was put into the cavity and brought out through an opening in the bone flap and scalp Postoperatively, the patient was treated with penicillin irrigations through the catheter and instillation of penicillin into the subarachnoid space via the lumbar route in addition to intramuscular injections He has been well since discharge from the hospital He had some seizures postoperatively and was therefore put on an anticonvulsive regime Needless to say, this must have been a metastatic abscess We searched for the primary focus of sepsis, but none was found We still do not know how this abscess got into the brain

DR KUBIK A small biopsy specimen consisted of brain tissue in which there was infiltration suggesting an acute process with polymorphonuclear leukocytes There was no fibroblastic capsule

DR MICHELSEN Because of the close proximity to important cortical centers we believed that excision of the capsule would not be advisable at that time

was no history that suggested uremia, and there was a persistence of Jacksonian seizures. I should therefore assume that this patient had an anatomic lesion somewhere within the skull.

What is the localization? The first thing to consider is the localizing symptoms given in the history. There were definitely Jacksonian seizures in the beginning, which frequently went over into general convulsions. These Jacksonian seizures indicate clinically definite localization in the left side of the brain. I think that we can be more accurate and say that the focus was low in the left temporo-parietal region, because the lips and the face were first involved. The aura of smell and taste is a definite sign of irritation of the hippocampal region. The headache was primarily on the left side, that is not, of course, a dependable sign for localization, but when it agrees with other things, the headache is often in fairly close proximity to the lesion.

The next symptom to comment on is the aphasia. From the clinical point of view aphasia is a localizing symptom of considerable value. Presumably this man was right handed, and the left side of the brain is therefore indicated. There is no long description of the aphasia, but the record states that it was "nominal." There was also slurring of the speech. That was probably something else and on the motor side of the paresis. Aphasia, primarily nominal, is characteristically seen in lesions of the temporal lobe. There are therefore a good many symptoms and signs on the clinical side alone indicating a lesion that could have been covered roughly by the palm of the hand and was low in the parietal region and primarily motor—although with a sensory overflow after an attack, since it is stated that the patient did not know where things were in his hand, and the aphasia and the aura point to the same region. The lesion may have extended farther, but I prefer to think that the later disturbance was an overflow from pressure or following a seizure and that the lesion itself did not involve the whole parietal region.

The pneumogram is not so conclusive as I thought it would be from the description, but no doubt it is true that there was some displacement of the brain to the right. I do not see how we can escape the conclusion that this was an anatomic lesion of considerable size in the region spoken of and confirmed more or less by the pneumogram. The x-ray films of the skull itself are not mentioned, but I think that they were essentially normal. Is that correct?

DR MICHELSEN: Yes.

DR AYER: What are the etiologic possibilities for such an expanding lesion?

The first group of conditions includes tumors, which are the most frequent in such cases. I shall take them up in a moment. The next is an abscess. Could this have been an abscess? That is not a rare cause of these symptoms, with the exception

perhaps of the aura of smell and taste, which is unusual in abscess, because probably 9 out of 10 cases come from the ear, which is not mentioned as having been abnormal. There was no discharge from the ear, the patient did not have chronic otitis media. Such abscesses invade the temporal lobe much farther posteriorly and do not give the picture that this patient presented. I am against the diagnosis of abscess because there was no chronic ear condition, because of the presence and importance of the aura of taste and smell and because of the spinal fluid, which showed no cells and which should have shown cells if an abscess had been present. Cysts are rare, especially hydatid cysts. No one has mentioned the liver in this case, and I think that if this had been a cyst the liver would have been enlarged. I have no further comment on cysts.

Granulomas should be considered. The granulomas we have seen have usually been in the upper part of the brain. I do not recall seeing any in this particular location, although I do not know why they should not occur there. The blood Wassermann and Hinton tests are not recorded, but I assume that they were negative. There is nothing in the history and nothing in the examination otherwise to indicate syphilis.

Could this have been a collection of blood? Two types could cause these symptoms. In acute hemorrhage there is sometimes an intracerebral blood clot, which acts in this way. There was nothing in the history to suggest it. There was no blood in the spinal fluid, which there might well have been, and the patient would surely have been sicker than he was, for he was normal between the intervals of convulsions. This I should not expect with an intracerebral collection of blood. The most frequent collection of blood, however, is extracerebral, usually subdural hematoma, which is a bugbear that we often meet. There is a note, which I think is a red herring, that the patient had sustained an injury to the head five years previously, it was apparently not severe but could account for the later development of subdural hematoma. In my experience, however, the mechanism of growth of subdural hematoma should produce these symptoms within a year, usually much sooner, with a lucid interval for months prior to development of symptoms. Five years is long enough to make it most unlikely that subdural hematoma exists. Moreover, these subdural collections are almost always higher in the parietal area. I therefore believe that a subdural collection of blood is unlikely.

The most frequent cause of these expanding lesions is a tumor. There is nothing in favor of metastasis that I can see. Metastatic tumor may be single in the brain but is usually multiple. In a large percentage of cases the lung also shows

developed. These had been relieved, and he was again well until four days before admission, when he noted the onset of jaundice. The important physical findings were that the patient was jaundiced and that he had a large liver.

It would be helpful to know what the region of the prostate felt like, but the previous operative procedure made this impossible. The problem resolves itself into the differentiation of the causes of jaundice and we turn to the laboratory for aid. A white-cell count of 15,000 is reported. This is consistent with the finding in obstructive jaundice or intrahepatic disease with considerable destruction of parenchymal tissue. The findings of bile in the urine and chalk-white stools, together with a blood cholesterol of 403 mg and an alkaline phosphatase of 70 units per 100 cc, point to an obstructive jaundice. The alkaline phosphatase is usually elevated in obstructive jaundice and is not generally high in cases of intrahepatic liver disease without an obstructive component. On the other hand the highest phosphatase I have ever seen was in a patient with biliary cirrhosis, in whom no definite obstruction had ever been demonstrated.

The urinary symptoms and findings were obviously due to an obstruction in the urinary tract, with superimposed infection. From the evidence at hand this obstruction was at the base of the bladder and the region of the prostate, possibly involving the right ureteral orifice.

The x-ray films provide little definite information. The upper gastrointestinal tract appears to have been essentially normal except for some deformity of the duodenal cap, which may or may not represent an old ulcer. I do not see anything in the region of the head of the pancreas. The mass described in the lower abdomen is in the region of the bladder. This could be due to a bladder full of urine, and I should like to know whether or not the clamp that is visible in the region of the catheter was attached to the catheter or not. I am inclined to believe that the mass represents something more than a full bladder because of the previously mentioned urinary symptoms and findings.

If the report of the physical examination is correct, this man had a tremendously large liver, and on this basis alone one suspects something more than primary parenchymal disease in that organ. In discussing the possibilities I think that it might be said that although biliary cirrhosis cannot be ruled out, it is not likely if the findings of a mass in the lower abdomen and the urinary symptoms are to be fitted into the same diagnosis. In any event one possibility is biliary cirrhosis and benign prostatic hypertrophy, with hydronephrosis on the right and superimposed pyelonephritis. A second, likelier diagnosis is a malignant tumor, such as carcinoma of the bladder, with metastases to the liver and to the extrahepatic biliary tract. A third

possibility is that this patient had metastases from the original lesion into the lymph nodes in the region of the base of the bladder, causing bladder-neck obstruction and obstruction in the region of the right ureter, and also metastatic spread to the liver. Metastasis to the liver from primary carcinoma of the rectum is usually a late manifestation, although it can occur early. If this patient were from Egypt rather than Bermuda one would have to consider *Schistosoma haematobium* as a cause of cancer of the bladder, with metastatic spread to the liver. This, however, is extremely unlikely. The vague digestive disturbances such as postprandial distention are, I think, perfectly consistent with the degree of liver involvement. The fact, which is mentioned twice, that there was some delay in recurrence from the colostomy enemas does not impress me in view of the negative examination after a barium enema.

In conclusion, I believe that this patient had a malignant tumor with metastases to the liver. I believe that the jaundice was partially due to obstruction of the major radicles of the biliary tree by metastases. This may have been at the porta hepatis, or it may have involved the common duct. The size of the liver suggests that it was full of metastases, and there may have been enough obstruction of the bile canaliculi due to metastases to cause the jaundice. I should not expect white stools however, unless there was obstruction of the hepatic or common bile duct. I suppose that primary carcinoma of the liver could have been present, with the urinary findings on an entirely separate basis. I do not understand why this case is being discussed here today if this were a simple case of metastases to the pelvic floor and to the liver from the original adenocarcinoma. Therefore, I put as my first possibility primary carcinoma of the bladder causing bladder-neck obstruction and interference with drainage of the right ureter, with secondary obstruction in the bladder and kidney and with metastases to the liver and probably elsewhere.

DR BENJAMIN CASTLEMAN: The first operation performed at this admission was a peritoneoscopy by Dr Edward B. Benedict. He found a markedly enlarged liver, whose surface was mottled, gravis green and smooth. No carcinomatous implants were seen. The gall bladder was dilated to three or four times the normal size. The rest of the peritoneal cavity, including the pelvis, was inspected by putting the patient in the Trendelenburg position. A biopsy of the liver was taken.

Have you any comment, Dr Ellis?

DR ELLIS: This is further evidence for obstruction of the common duct and against interference with the manufacture and flow of bile into the gall bladder. There may have been a common-duct stone, but there were few symptoms of it other than

DR KUBIK Occasionally, we see an abscess like this in which no focus of infection can be found. Most cerebral abscesses are a result of sinus infection, otitis media or chronic suppuration in the lungs. We have had two or three fatal cases in which the sinuses, ears and lungs appeared to be normal and in which the source of the infection could not be determined.

DR WHITE Has this patient had postoperative seizures? In our experience a great many patients with abscesses have seizures both in the acute stage and after operation.

DR MICHELSEN Yes, he had some, but we put him on an anticonvulsion regime, soon after the operation, and I suppose that it worked all right.

DR AYER I do not see how the spinal fluid could have been normal. Was it examined carefully?

DR MICHELSEN The fluid was examined four times, on one occasion I examined it myself, and only 1 leukocyte per cubic millimeter was found.

DR AYER That is unusual in abscess.

DR MICHELSEN Of course, the duration was short — only ten days.

DR AYER Yes, that often happens in tumor.

DR KUBIK In a case of glioblastoma some time ago the entire duration of symptoms was only twelve days. Such a rapid course is rare but does occur occasionally. We have had a few other cases of abscess without cells in the spinal fluid, but those, I believe, were old, chronic abscesses. One would expect cells in an acute case such as this.

CASE 33262

PRESENTATION OF CASE

A seventy-one-year-old Bermudian Negro entered the hospital because of jaundice.

Two and a half years before admission the patient had undergone a combined abdominoperineal resection for an adenocarcinoma (Grade II) of the rectum. On microscopical examination the regional lymph nodes contained no tumor. After operation, the patient was followed in the Out Patient Department periodically for over two years. The colostomy functioned well, and he had no complaints except slight dysuria, narrowing of the urinary stream and dribbling and nocturia. Four months before admission he had a two-week episode of pain in the right flank and pyuria. After catheterization he failed to return to the clinic. Four days before entry the patient's sister noticed that the eyes were yellow. In retrospect he recalled that the urine had left greenish stains on the underclothes for several months. The stools had been lighter than formerly but were still slightly brown or yellow. The appetite was poor, and the patient had been troubled with distention and flatulence after eating. Later he noted that the daily enema returns from the colostomy were delayed over periods of two hours.

There had been no abdominal pain, nausea, vomiting or headache. There was no history of itching, bleeding or drug intake.

Physical examination disclosed generalized vitiligo. The pale areas and the scleras were yellow. The liver border extended 6 cm. below the costal margin, the upper limit of dullness being at the fourth rib. Neither the gall bladder nor the spleen could be palpated. The colostomy appeared normal. A rather large, reducible, direct hernia protruded in the left inguinal region. The perineum had healed.

The temperature was 98.8°F, the pulse 70, and the respirations 20. The blood pressure was 120 systolic, 85 diastolic.

Examination of the blood revealed a hemoglobin of 13 gm. and a white-cell count of 15,000, with 72 per cent neutrophils. The urine gave a +++ test for bile and a ++ test for albumin, and the sediment contained 50 white cells per high-power field. The stools were chalk white and semiformed. The van den Bergh reaction was 16.8 mg. per 100 cc. direct, and 24.8 mg. indirect. The cholesterol was 403, the phosphorus 2.8, the nonprotein nitrogen 36 and the calcium 8.0 mg. per 100 cc. The alkaline phosphatase was 70 units per 100 cc. The total protein was 5.3 gm. per 100 cc., with 3.1 gm. of albumin and 2.2 gm. of globulin. The prothrombin time was 25 seconds (normal, 17 to 19 seconds).

X-ray films of the chest were normal. In a gastrointestinal series the duodenal cap appeared markedly narrowed at the tips. There was a slight pressure defect at the point where the superior mesenteric vessels crossed the duodenum, but no definite mass was visualized.

In the hospital the patient's condition remained about the same, although the jaundice increased slightly. Filiform catheters were passed through an obstructed prostatic urethra with difficulty, and constant drainage was instituted. He continued to have crampy postprandial distention, and it took two hours for the daily enema to return. A barium enema passed through the colon into the terminal ileum without evidence of obstruction. A loop of ileum descended into the left inguinal region. Above and medial to this loop was a defect caused by pressure of a soft-tissue mass that was not clearly visualized and lay in the region of the prostate or of the previous operative site in the area of the rectum. This mass measured approximately 7 cm. in diameter.

An operation was performed on the thirteenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR DANIEL S. ELLIS In summary, this patient had undergone an abdominoperineal resection for adenocarcinoma of the rectum two and a half years before admission. He had been well until four months before admission, when urinary symptoms

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

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MATERIAL should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

THE BOSTON DISPENSARY

THE Boston Dispensary in March of this year, with Surgeon General Parran as guest speaker, celebrated a little tardily its one hundred and fiftieth anniversary. This sesquicentennial celebration—the half century is still an important landmark in our young country—serves to recall certain events in the history of the Dispensary, as well as its present needs.

The Dispensary, we are reminded, came officially into being at the Boston Chamber of Commerce on September 11, 1796, with the acceptance by a group of citizens of a report from Dr. Oliver Smith and Mr. William Tudor providing rules and regulations for the proposed institution. The third such dispensary in the country and today the only

survivor of the three, the Boston Dispensary was also the first medical charity in New England.

Coming into existence less than twenty years after the signing of the Declaration of Independence, the Dispensary followed by fifteen years the foundation of the Massachusetts Medical Society—the first state society in the country with a continuous existence—and antedated by sixteen years the establishment of the *New England Journal of Medicine and Surgery* and by twenty-five years the opening of the doors of the Massachusetts General Hospital.

Thomas Bartlett's apothecary shop on Corn Hill became the first headquarters of the organization and here hung its first signboard, bearing the picture of the Good Samaritan to represent its functions. Its three main principles were embodied in the report submitted by Dr. Smith and Mr. Tudor:

The sick, without being pained by a separation from their families, may be attended and relieved in their own houses.

The sick can, in this way, be assisted at a less expense to the public than in any hospital.

Those who have seen better days may be comforted without being humiliated, and all the poor receive the benefits of a charity, the more refined as it is the more secret.

The services of the Dispensary increased as the town and the Commonwealth prospered. In 1801 it was incorporated, twenty years later, on the principle that "the moral effect of a clean skin is often more potent in the treatment of ailments than the administration of drugs," it procured a bathtub to be located conveniently "in some central place." In 1856 its clinic for ambulatory patients was opened, in 1873 the country's first clinic for syphilis and the first dental clinic, and in 1899 the first pulmonary clinic.

The Boston Floating Hospital, finally grounded, was established on land in conjunction with the Dispensary in 1929, and at the time of this union plans for the New England Medical Center, to include Tufts College Medical and Dental schools were formed. The Joseph H. Pratt Diagnostic Hospital was added in 1938.

Like all the charitable institutions that have carried on through the war years without expansion, the Dispensary is now in need of funds to

jaundice The large liver still puzzles me, and I think that it was larger than that usually found in biliary cirrhosis I am probably wrong, but I shall stick to the original diagnosis of metastasis to the liver, with tumor obstructing the common duct In the absence of positive peritoneoscopic findings of tumor in the pelvis the chances favor metastases from the original carcinoma of the rectum, even after two and a half years

DR WADE VOLWILER I saw this patient after the peritoneoscopy and believed that the distended gall bladder, the elevated cholesterol, the high alkaline phosphatase and the absence of splenomegaly indicated common-duct obstruction by tumor My best bet was lymph-node metastases from the carcinoma of the rectum I also believed that there were hepatic metastases not visible by peritoneoscopy

CLINICAL DIAGNOSIS

Carcinoma of head of pancreas

DR ELLIS'S DIAGNOSIS

Metastatic carcinoma of liver and lymph nodes around extrahepatic biliary ducts from carcinoma of bladder or from carcinoma of rectum

ANATOMICAL DIAGNOSIS

Metastatic adenocarcinoma of lymph nodes around bile ducts from previously resected adenocarcinoma of rectum

PATHOLOGICAL DISCUSSION

DR CASTLEMAN The liver biopsy showed an extreme grade of bile stasis and obstructive cirrhosis, but no evidence of carcinoma

Following this report the patient was explored with a preoperative diagnosis of carcinoma of the head of the pancreas, this diagnosis being chosen probably because of the slight pressure on the duodenum visualized on the x-ray films At operation the liver was large and slightly granular but showed no evidence of carcinoma The gall bladder was tremendously dilated, measuring about 10 cm in diameter Surrounding and compressing the extrahepatic bile ducts were nodules of tumor that proved microscopically to be adenocarcinoma characteristic of the type seen in the colon

continue the fulfillment of its destiny. Other charities may have an equal claim on the generosity of the public, surely none can have a greater

REFSUM'S DISEASE

A FAMILIAL disease, not hitherto described, has recently been reported from Norway.* The syndrome was observed in two Norwegian families, not related to each other. In one, a brother and a sister were affected, in the other, two sisters and their cousin. The chief symptoms were hemeralopia (retinitis pigmentosa), polyneuritis, ataxia and other cerebellar manifestations. Both patients in the first family died suddenly of respiratory paralysis. The pathologic changes were limited to the brain, with degeneration in the lipid content and pigment anomalies. The lesions closely resembled those found in Niemann-Pick disease and in familial amaurotic idiocy.

The first clinical symptoms were limitation of the fields of vision and hemeralopia. These complaints often preceded difficulty in walking, due to the ataxia, by many years. Paresthesias were most marked in the hands and feet. In some cases the pain was said to be "burning" or "shooting" in character. No case showed mental manifestations. The ataxia was of the cerebellar type, and other vague cerebellar symptoms were occasionally present. The cerebrospinal fluids contained large amounts of protein, without a corresponding increase in cells, findings somewhat similar to those in the Guillain-Barré syndrome. Three patients had sinus tachycardia by electrocardiographic examination. Others had abnormalities of the pupils, deafness or epiphyseal dysplasia. The syndrome was considered hereditary, probably of a simple recessive type. When large amounts of vitamins were given, at least one patient showed objective improvement.

*Refsum, Sigvald. *Heredopathia Atactica Polyneuritisformis*. 303 pp. Oslo: J. G. Tanum, 1946.

MASSACHUSETTS MEDICAL SOCIETY

ANNUAL REGISTRATION IN INDIANA

Indiana has recently passed a law requiring annual registration of physicians, which becomes effective on July 1. The fee for those who are nonresidents is \$10.00, and the licensee must register before August

31. Since failure to register results in automatic cancellation of the certificate, all who hold Indiana licenses and wish to retain them should obtain application for registration from the State Board of Medical Registration and Examination, K of P Building, Indianapolis 4.

JOSEPH GARLAND, Secretary

ANNUAL GOLF TOURNAMENT

The winners at the annual golf tournament of the Massachusetts Medical Society, which was held at the Woodland Golf Club on the afternoon of May 15, were as follows: low gross, R. J. Nugent, second gross, M. Sargent, low net, A. D. Crowell, second low net, G. Quigley.

MISCELLANY

NOTE

Dr. Duncan E. Reid will become William Lambert Rich, son Professor of Obstetrics at the Harvard Medical School and obstetrician-in-chief to the Boston Lying-in Hospital July 1. He succeeds Dr. Frederick C. Irving, who resigns both positions as of December 31, 1946. Dr. Reid has served continuously on the staff of the Lying-in Hospital since 1911 and joined the staff of the Harvard Medical School in 1918. Born in Burr Oak, Iowa, on December 22, 1905, he graduated from Ripon College in 1927. He received his medical degree from Northwestern University in 1932 and served as an intern and resident at the Passavant Memorial and St. Luke's hospitals of that city before coming to Boston.

CORRESPONDENCE

LABORATORY TRAINING IN PARASITOLOGY

To the Editor: The *Journal* is to be congratulated on excellent editorial, "Diagnosis of Amebiasis by Stool Examination," that appeared in the April 24 issue. It demonstrates a thorough understanding of the laboratory problem involved in this difficult examination. It agrees closely with what we believe and teach in the Parasitology Branch, Laboratory Division of the Public Health Service. In the editorial mentions "the need for improved training of hospital laboratory technicians in the performance of examinations," you may be interested in knowing about our laboratory training program.

Since October, 1945, we have been conducting a six-week course in the laboratory diagnosis of parasitic diseases, the sessions having been completed. This course is open to all grades of laboratory personnel, and although at the present time our first responsibility is to the laboratories of state and local health departments, we are glad to accept persons from private hospitals and laboratories as vacancies occur. There is no tuition or laboratory fee, but travel and living expenses must be paid for by the individual or his employer.

In addition to the parasitology course, the Laboratory Division offers an extension service of parasitologic material. This service involves monthly shipments of specimens that are numbered and accompanied by a key to the correct diagnosis. This service is also open to state and local health departments and to the students who have attended our course in Atlanta.

R. A. VONDERLIEP
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(Notices on page xix)

